NDA 20-920 Natrecor ® (nesiritide)
Reviewer Abraham Karkowsky, M.D., Ph.D. _____
Date 4/25/01

There will be several additional documents that will constitute the completed review. Only studies 704.339 (VMAC) and 704.329 (PRECEDENT) are reviewed in this package. Several analyses have yet to be formally included into this document for the two studies that have been reviewed. There was no attempt to incorporate the results of previous studies into a integrated safety and efficacy document.

Table of Contents:

Study: # 704.339

Title of Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Hemodynamic and Clinical Effects of Natrecor® (nesiritide) Compared With Nitroglycerine Therapy for Symptomatic Decompensated CHF (The VMAC trial).

Investigator and Sites:

Table 1. Investigators and sites.

Site # 679 Aaron, M.F., MD and Bourge, RC, MD U of Alabama at Birmingham Birmingham ,Al	Site # 615 Abraham, W, MD U. of Cincinnati Med Center Cincinnati, OH	Site # 668 Bank, AJ, MD St. Paul Heart Clinic, PA St Paul MN	Site # 657 Berk, M, MD Cardiovascular Research Institute of Dallas Dallas, TX
Site # 637 Bhat, G., MD U of Louisville Research Foundation Louisville, KY	Site # 638 Browne, K, MD Watson Clinic Lakeland FL	Site # 561 and # 697: Berger, A, MD Beth Israel Deaconess Med Center Boston, MA	Site # 683 Chu, A., MD HeartCare Midwest Peoria, IL
Site # 679: Cobb, FR, MD Durham VA Med Center Durham, NC	Site #674 Cotts, W, MD Northwestern Memorial Hospital Chicago, IL	Site # 620: DeMarco, T, MD U Calif, SF Med Center SF, CA	# 502 Dennish, G, MD San Diego Cardiovascular Research Associates Encinitas, CA
Site # 618: Dinerman, J, MD Jacksonville Heart Cetner, Jacksonville, Fl	# 570 and #676 El Hafi, S, MD Med Tech Research, Inc Houston, Tx	# 554 and # 695 Elkayam, U.; MD LA County, USC Med Center LA, CA	# 519 Feldman, R., MD MediQuest Research Group Ocala, Fl
# 543 Fishbein, D, MD U of Washington Med Center Seattle, WA	# 585 Ford, LE, MD Roudebush Med Center Indianapolis, IN	Site # 678 Ghali, J, MD Cadiac Ctrs of LA, L.L.C. at Willis Knighton Heart Inst Shreveport,LA	Stie # 671 Goldsmith, SS, MD Hennipen County Med Center Minneapolis, MN
Site # 681 Goldsmith, SS, MD U of MD Med System Baltimore, MD	Site # 538 Greenspan, M, MD Buxmont Cardiol Associates Lifemark Medical Center Sellersville, PA	Site # 642 Hall, J, MD Med Reserch Consortium at Winona Memorial Hosp Indianapolis, IN	Site # 357 Hare, J, MD The Johns Hopkins Hospital Baltimore, MD
# Site #524 Harlamert, E, MD Community Hospital East Indinapolis, IN	Site # 543 Hassapoyannes, C, MD Dorn Research Institute Columbia, SC	Site # 663: Haught, WH, MD The Heart Center Huntsville, AL	Site # 355: Hershberger, R., MD Oregon Health Sciences University Portland, OR
Site # 686 Hettleman, BD, MD Dartmouth Hitchcock Med Center Lebanon, NH	Site # 666 Hill, JA, MD U of Florida Health Sci Center Gainesville, FL	Site # 551 Hoagland, PM,MD San Diego Cardiac Center Research Department San Diego, CA	# Site # 382 Johnson, AD, MD Scripps Clinic La Jolla, CA
Site # 356 Kao, W, MD Rush-Presbyterian-St Lukes Med Center Chicago, IL	Site # 567 Karlsberg, R, MD Cardiovascualr Res Institute of Southern CA Beverly Hills, CA	Site # 627 Koren, M, MD Jacksonville Center for Clinical Research Jacksonville, FL	Site # 367 Kukin, M, MD Mt Sinai Med Center New York, NY

Site # 693 Lamas, G, MD Mt Sinai Med Center NYC, NY	Site # 369 LeJemtel, T, MD Albert Einstein Hospital Bronx, NY	Site # 605 Liang, C, Ph.d., MD U of Rochester Med Center Rochester, NY	Site #370 Lui, CY, MD U of Ariz Health Science Center Tucson, AZ
Site # 540 Mallon, SM, MD U of Miami/Jackson Memorial Med Center Miami, FL	Site # 516 McGrew, FA, MD The Stern Cardiovascular Center Memphis, TN	Site # 687 and Site # 711 McIvor, ME, MD and Schyler, G, MD The Heart Inst of St Petersburg St Petersburg, FL	Site # 647 Miller, AB; MD U of Florida Health Science Center Jacksonville, FL
Site # 677 Moskowitz, R, MD Motefiore Med Center Bronx, NY	Site # 572 Oren, R.M, MD Univ of Iowa Hospitals and Clinics Iowa City, IA	Site # 547 Promisloff, S, MD Hillsboro Cardiology Hillsboro, OR	Site # 628 Reddy, H, MD U. of Missouri Health Science Center Colombus, MO
Site # 688 Roark, SF, MD Cardiology Associates of Gainesville Gainesville, FL	Site # 545 Schocken, D, MD USF College of Med Tampa, FL	Site # 675 Silver, MA, MD Christ Hospital Med Center Oak Lawn, IL	Site # 636 Stevenson, LW, MD Brigham and Women's Hospital Boston, MA
Site # 560 Torre, G, MD Baylor Colege of Medicine Houston, TX	Site # 360 Varhese, J, MD George Washington Med Center Washington, DC	Site # 508 Vaska, K, MD U of SD School of Medicine Siouz Falls, SD	Site # 656 Vranian, R, MD Cardiovascular Medicine of Virginia at Pratt Medical Center LTD Fredricksburg, VA
Site # 503 Wagoner, L, MD U of Cincinatti Med Center Cincinnati, OH	Site # 579 Walsh, MN, MD The Care Group LLC Indianapolis, IN	Site # 539 Wilson, D, MD U of Kansas Med Center Kansas City, KS	Site # 580 Wilson, JR, MD Vanderbilt U Med Center Nashville, TN
Site # 667 Young, J, MD The Cleveland Clinic Foundation Cleveland, OH	Site # 680 Zafari, AM, MD, Ph.D VA Medical Center IIIB Decatur GA		

Formulations:

The Natrecor used in this study was produced using recombinant DNA technology (Lot K0003A). The formulation consists of Natrecor (2.5 mg), mannitol (20 mg), citric acid monohydrate (2.6 mg), and sodium citrate dihydrate (2.94 mg).

Dates of the study:

The specific dates of the protocol are shown in table 2. The amendments were only incorporated before a substantial portion of the subjects was enrolled.

Table 2. Important study dates

Original Protocol	4 August 1999
First Amendment	28 April 2000
Second Amendment	31 August 2000
First Subject Enrolled	26 October 1999
Last Subject Completed	25 August 2000
Blind Broken	12 Sep 2000

Oversight Committees: The protocol stipulated the formation of a Data Safety Monitoring Committee consisting of three experts in the field of either heart failure and/or clinical research and a statistician who are independent of Scios Corporation. The data reported to the DSMB is to include all deaths, myocardial infarctions, cerebrovascular accidents and acute renal failure requiring dialysis that occur within the 30 day period of the start of infusion.

Treatment groups: Subjects are to be stratified, with approximately half the subjects to be catheterized and the other half treated without a catheter in place. Those who enter with a right heart catheter in place are to be included in the catheter stratum. Other subjects will be allocated to either catheter or non-catheter treatment based on the investigator's usual treatment.

There are five different treatments
Group 1: Placebo (3 hours) followed by IV nitroglycerine (after 3 hours).
Group 2: Placebo (3 hours) followed by IV Natrecor (after 3 hours).
Group 3: IV Nitroglycerine
Group 4: IV Natrecor fixed dose
Group 5: IV Natrecor adjustable dose (catheterized stratum only)

Since Natrecor binds to heparin, non-heparin coated intravenous tubing must be used.

The initial dose of Natrecor is to consist of a bolus of 2ug/kg over approximately 60 seconds followed by the constant infusion at 0.01 ug/kg/min. The treatment regimens for both the Natrecor fixed and Natrecor adjustable doses were exactly the same for the first three hours.

After the first three hours, those randomized to the fixed dose regimen received a constant dose of 0.01 ug/kg/min for the duration of therapy. For those who are randomized to the adjustable dose Natrecor, the dose could be increased if the PCWP was $\geq$ 20 mm Hg and the SBP was $\geq$ 100 mm Hg. The increase consisted of a bolus of 1 ug/kg over 60 seconds followed by an increase of the infusion rate by 0.005 ug/kg/min. The adjustment can be made every 3 hours to a maximum dose of 0.03 ug/kg/min. Each increase is predicated on the same PCWP and SBP criteria.

For those treated with nitroglycerin, the dose regimen is to reflect the investigator's usual regimen for this drug.

From two hours prior to the start of infusion through the 3-hours placebo controlled period, the following medications must be withheld.

- Continuous intravenous diuretics
- Nitroprusside
- IV ACE inhibitors
- Milrinone
- New infusion of dobutamine
- New infusion of dopamine
- Non-blinded nitroglycerine

Ongoing dobutamine and dopamine may be continued but the dose is not to be increased.

From the end of the 3-hour placebo-controlled period, the following medications should be withheld:

- Nitroprusside
- Milrinone
- IV ACE inhibitors
- Non-blinded nitroglycerine

Non intravenous cardiac medications are allowed as needed. The investigator is to be made aware that vasodilators may exacerbate the hemodynamic effect of the blinded treatments. Oral diuretics may be used at any time. If an intravenous diuretic is needed, a bolus dose rather than a constant infusion regimen is preferred.

Contingencies related to dosing:
Symptomatic hypotension: Both drugs (active and dummy) are to be stopped for symptomatic hypotension. Treatment of the hypotensive event is initiated (i.e. normal saline) and the specifics of the hypotensive event are recorded. Once the subject is stabilized, the dose of the study drug can be restarted at a rate 30% less than the infusion at the time of the hypotensive event (no bolus for Natrecor).

Reduction based on clinical response: The infusion rate should be decreased if:

- SBP < 90 mm Hg (unless this BP is appropriate for that subjects)
- PCWP < 12 mm Hg.

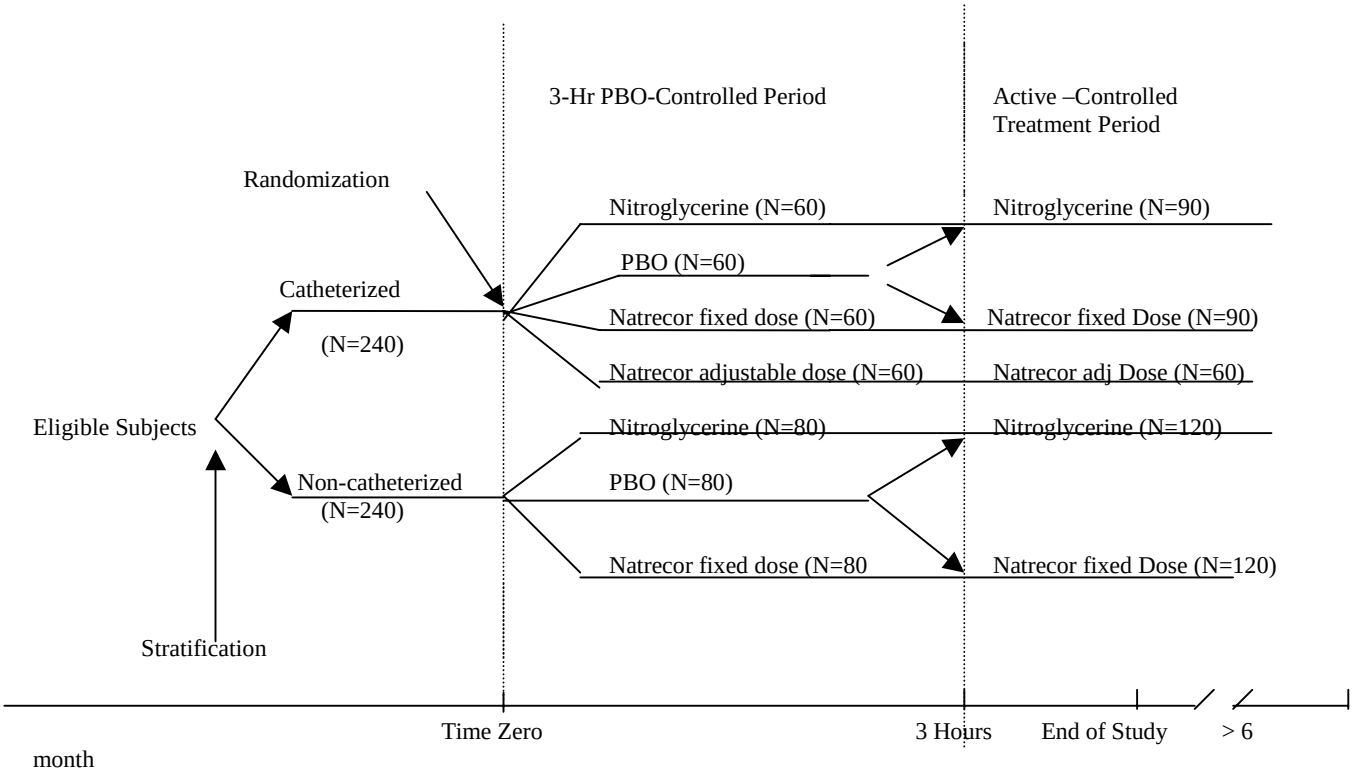
Both infusions should be decreased appropriate to the severity of the hemodynamic response. The Natrecor dose should be decreased by 30%, the nitroglycerine dose should be decreased by the investigator's usual practice. The specifics of the event should be recorded. At the discretion of the investigator, the drug can be restarted. For Natrecor, the dose should be decreased by 30% (no bolus) of the dose producing the above hemodynamic response. For nitroglycerine the dose should be restarted per standard practice of the investigator.

Worsening CHF: The investigator should first optimize the index study treatment. Oral or permitted intravenous drugs should next be added. During the initial three hours of the infusion, the administration of intravenous cardiovascular drugs should be used only if urgently needed. The preferred next medication is dobutamine. During the active controlled period (after hour 3) those subjects recently crossed-over from placebo should have the dose optimized with active drug before adding on other medications.

Long-term continuation of study drug: Some subjects may be continuously treated in a blinded-fashion for > 30 days. After the initial 30 days, subjects at the discretion of the investigator could be treated with open-labeled Natrecor. For these subjects, dosing increases and decreases are predicated on the same regimens as those treated with adjustable dose Natrecor.

A schematic representation of the study is shown as Figure 1. Four of the treatments were employed among those not catheterized (all except the IV Natrecor adjustable dose) and all were employed among catheterized subjects.

Figure 1. Schematic of study 704.339



Protocol:

Inclusion Criteria:

A total of 480 subjects were to be enrolled equally, distributed between catheterized and non-catheterized subjects.

Eligible subjects were those:

- Greater than 18 years old.
- Have dyspnea at rest, while supine or immediately upon minimal activity such as talking eating or bathing.

  These subjects must have cardiac disease as the etiology of their symptoms by demonstrating two of the following:
  - JVD;
  - Paroxysmal nocturnal dyspnea or 2-pillow orthopnea within 72 hours of entry;
  - Abdominal discomfort (↓appetite or nausea) due to hepato-splenic congestion;
  - Chest X-ray consistent with heart failure;
- Elevated cardiac filling pressures (estimated among those non-catheterized) and > 20 mm Hg among those who are catheterized;
- Require hospitalization and IV therapy for at least 24 hours for the treatment of acute decompensated heart failure;
- Understand and sign an informed consent;

- Post-MI subjects are not excluded.

Exclusion Criteria:

Subjects will be excluded for:

- SBP < 90 mm Hg;
- Cardiogenic shock, volume depletion, or any other clinical condition that would contraindicate the administration of an IV agent with vasodilatory properties;
- Recent PCWP < 20 mm Hg;
- Clinically unstable and cannot tolerate catheterization or a 3-hour period off medication;
- Subjects who cannot tolerate withholding nitroglycerine (e.g. acute coronary syndrome);
- Received Viagra® (suldenafil) within 24-hours of start of study;
- Known methhemoglobenemia;
- Allergic reaction to nitrates, nitroglycerin or Natrecor;
- Requiring mechanical ventilation;
- Potential or actual pregnancy;
- Unlikely to survive 30-35 days;
- Recent treatment with investigational drug;
- Unable or unwilling to comply with the study requirements.

Randomization:

The investigator will decide whether the subject is to have a right-heart catheter in place for the management of their CHF. Once this decision is made, the subject is randomized among the different treatments. The process required the pharmacist to phone an automated telephone randomization system to receive the treatment assignment.

Blinding:

The study was performed as a double-dummy design. Two bottles one containing nitroglycerine or placebo and the second bag containing Natrecor or placebo was attached to a "Y" connector at the infusion site or infused through two different infusion sites. After the first three hours of treatment, the placebo group was to be unblinded and the subjects advanced to the second randomized treatment (i.e. to either nitroglycerine or Natrecor fixed dose) in a blinded manner. In order to protect symptom assessment from contamination by the knowledge of the hemodynamic effect, hemodynamic measurements were to be collected only after the dyspnea measurements and global assessment were performed. The investigator was not to discuss hemodynamic measurements within the hearing range of the subject. A log was kept reflecting the time of unblinding. The treatment of subjects treated either with nitroglycerin or Natrecor was not unblinded but referred to as "on active treatment" and continued after the three-hour time point.

The on-site pharmacist was unblinded as to therapy.

Catheterization Procedures:

A right heart catheter is placed and the appropriate position confirmed by x-ray or fluoroscopy. When stabilized, hemodynamic measurements are to be performed at 5-15 minute intervals until two sets of PCWP measurements are within 15% of each other (not specified is whether the high or low value is to serve as the basis of this 15%). A PCWP $\geq$20 mm Hg is the only hemodynamic requirement for enrollment. Catheter placement and eligibility are to be

determined immediately prior to randomization. If ineligible, the subject should not be randomized. The catheter is intended to remain in place for at least 48 hours.

Primary End Point:

The primary objectives of the study are to compare the hemodynamic effect and clinical response of Natrecor to placebo at the 3-hour time point using the all treated, as randomized cohort of those receiving any study drug. Specifically, the two analyses are:

1) PCWP (catheterized subjects only).
2) Dyspnea evaluation (all subjects).

There are seven possible ratings for the dyspnea rating.

Markedly better = + 3
Moderately better = +2
Minimally better = +1
No Change =0
Minimally worse = -1
Moderately worse = -2
Markedly worse = - 3

The primary endpoints are the change from baseline at 3 hours during the infusion comparing Natrecor to placebo. For the study to be considered a success-both measurements must be significant at a $p < 0.05$. The two Natrecor groups (adjustable and fixed dose) are pooled for wedge pressure measurements. For dyspnea evaluation catheterized (adjustable and fixed Natrecor) and not-catheterized subjects will be pooled for the analyses. Observations are to be made prior to the unblinding of the treatments at the three-hour time point.

Since both analyses had to be statistically significant relative to placebo, no correction was made for the multiplicity of the end points.

For the primary analysis of PCWP, the data is limited to those catheterized. The method of analysis is a one-way ANOVA. A two-sided 95% confidence interval is constructed.

For the analysis of the dyspnea index a two –way ANOVA model with treatment and catheter use as factors. In addition a stratified two-sample Wilcoxon procedure (Van Eltern's test), stratified on right heart catheter use or an ordinal logistic regression using proportional odds model with cumulative logits will be used to assess the robustness of the primary analysis results.

No values were imputed for missing data.

Secondary Objectives:

The secondary objectives are to compare the hemodynamic and clinical effects of Natrecor with IV nitroglycerine and placebo. The hemodynamic parameters that will be assessed are the change from baseline of right atrial pressure (RAP), cardiac output (CO), pulmonary artery pressure (PAP), that fit within the specified time windows. Additional analyses (prespecified) are: the proportion of subjects whose dyspnea is improved at three hours (defined as markedly or moderately improved). A similar assessment will be made for the subject's global assessment.

The following specific measurements are included as secondary study objectives.

1) The effect of PCWP and dyspnea 1-hour after the start of study drug.
2) The onset of effect treatment on PCWP.
3) The effect on PCWP 24 hours after the start of study drug.
4) The overall safety profile.

For placebo subjects who are switched to the two active treatments, the baseline is considered the last measurement prior to switching. For the analysis comparing active treatments would be tested in the framework of an ANOVA model

The Cochran-Mantel-Haenszel test for general association with catheter use as the stratification factor or logistic regression, including treatment and catheter use as factors in the model, that will be used to assess dyspnea improvement at 3 hours. Two-way analysis of variance model, with treatment and catheter use as factors and the corresponding non-parametric procedures will be used for the symptom and global assessment evaluations at each follow-up time.

Additional Metrics:

This metric includes a comparison of the need for the addition of IV vasoactive agents and/or diuretics and the effect of adding such medication on the hemodynamic variables during the first three hours of the infusion. Use of a vasoactive drug is defined as either a new administration or an increase in dose of a continued intravenous regimen that includes dobutamine, milrinone, dopamine, nitroprusside, nitroglycerine, amrinone, epinehrine, norepinephrine or neosynephrine. A similar assessment will be made during the first 24-hours of the study.

Also measured are the mean change in body weight from baseline to 24 hours, total urine volume for the first 24 hours, hospital admissions during the first 30 days, deaths during the first 30 days, 90 days, and 6 months post-initiation of treatment.

The method of analysis for each of these additional analyses is the Cochran-Mantel-Haenszel test with catheter use as a stratification factor. For continuous measurements of efficacy, an omnibus F-test followed by pair-wise contrasts for an overall significant result will be applied to the data. The log rank test will be used for the comparison of the 30 day, 90 day and 6 month mortality between treatment groups. Cox proportional-hazard regression model, adjusting potential baseline or time-dependent covariates may be considered as deemed appropriate for the analysis of time to event data.

Other statistical Issues:

No interim analyses were planned for the study.

The power calculation for hemodynamic measurements was based on the unequal randomization of subjects to Natrecor (combine fixed and adjustable doses) versus placebo (2: 1 ratio), with 120 and 60 subjects /group respectively, this sized study has a 88% power to detect a 3 mm Hg drop in PCWP assuming a standard deviation of 6 mm Hg at an α=0.05.

For the dyspnea index, there were 200 subjects in the Natrecor group (catheterized subjects both adjustable and fixed infusion =120 subjects + non-catheterized subjects =80 subjects) and placebo catheterized and non-catheterized there were 140 subjects. The study has an 88% power to detect a 0.3 unit difference in the dyspnea scale, assuming a standard deviation of 0.8 at the significance level of 0.05. For the ordinal analysis the sponsor assumed that if the shifts for the treatment group were:

Table 3. Distribution of symptom improvement for power calculation

	+3=much better	+2= moderately better	+1= minimally better	0=No change	-1= minimally worse	-2= moderately Worse	-3= Much worse
Natrecor	5%	20%	25%	40%	5%	5%	0%
Placebo	0%	15%	20%	50%	5%	5%	5%

The Wilcoxon rank test would have a power of 86% to detect a difference between groups at an α=0.05.

Protocol-procedure timing:

The timing of specific procedures is shown in Table 4. Hemodynamic measurements were limited to those subjects who were catheterized. The dyspnea evaluation, the other efficacy metric was measured in all subjects and was collected frequently during the initial three hour placebo-controlled period, and also, albeit less frequently during the remainder of the study. Fluid intake and output data was also collected. Weight was measured at baseline and at the end of 24 hours. Mortality was collected monthly during the 6-month post-treatment phase. Hospitalizations were collected only till day 30.

Table 4. Procedures during study 704.339

			3-Hour Placebo-Controlled Period						Active-Controlled Treatment Period							Post-Treatment Period		
	Screening[1]	Baseline	0	15 min	30 min	1 hr	2 hr	3 hr	6 hr	9 hr	12 hr	24 hr	36 hr	48 hr	Inf end	Day 14-19	Day 30-35	Through 6 months
Informed Consent, Medical History, PE, Ht[2], Wt, Right Heart Cath.	X																	
Weight	X											X						
Concomitant Medications	X[1]	→	→	→	→	→	→	X[3]										
Cardiac Rhythm		X																
BP[11], HR[11]	X	X		X	X	X	X	X	X	X	X	→	→	→	X			
Respiratory Rate		X				X		X										
PCWP and PAP	X[4]	X[5]		X	X	X	X	X	X[12]	X	X	X[12]	X[12]	X[12]				
CO, RAP		X[5]				X		X				X						
Study Drug Administration[8]			X	→	→	→	→	X[9,10]	→	→	→	→[10]	→	→	X[13]			
Troponin, Creatinine Kinase-MB		X[6]																
Creatinine		X[6]										X			X[14]	X	X	
Fluid Intake/Output		X[7]	→	→	→	→	→	→	→	→	→	X						
Dyspnea Evaluation		X		X	X	X	X	X	X			X			X[15]			
Global Clinical Evaluation				X	X	X	X	X	X			X			X[15]			
Unblinding								X[9]										
Adverse Events			X	→	→	→	→	→	→	→	→	→	→	→	→	X[16]		
Serious Adverse Events			X	→	→	→	→	→	→	→	→	→	→	→	→	→	X[17]	
Mortality																	X[18]	X[19]

[1]Obtain within 24 hours before starting Drug.
[2]Catheterization subjects only.
[3]Hold restricted medication from 2 hours before start of study drug through the end of the 3-hour PBO-controlled period.
[4]Screening PCWP must be ≥ 20 and SBP ≥ 90 mm Hg.
[5]Obtain within 20 minutes before starting study drug.
[6] Obtain within 6 hours before starting study drug.
[7]The subject should try to empty their bladder within one hour before, and as close to the start of study drug as possible. Record all I/O for the 24 hours after the start of study drug.
[8] Administer study drug as per protocol.
[9]After all 3-hour assessments have been completed, call ATRS to determine whether subject on PBO or active drug. PBO will be switched.
[10] All subjects should continue study drug for 24 hours.
[11]Vitals are to be recorded at the above time point and every three hours. Vitals are also to be recorded upon increase or decrease of dose.
[12] PCWP should be recorded.
[13] Duration of study beyond 24 ours is left to the discretion of the investigator.
[14] Obtain daily through two days post infusion
[15] Obtain at time of drug discontinuation.
[16] For subjects who receive drug for ≥ 8 days, record 7 days post end of infusion.
[17] Though study day 30.
[18] Obtain on or after day 30.
[19] Obtain mortality status monthly through 6 months after randomization.

Results:

Patient Disposition:

A total of 498 subjects were randomized across 55 sites. Of these subjects nine, were not treated because they did not meet all inclusion/exclusion criteria at the time infusion was to begin. These subjects were excluded from all analyses (including safety and mortality).

The specifics of those who did not received treatment were as follows.

- Subject # 642-501 (randomized to Natrecor, fixed dose) had a blood systolic pressure below 90-mm Hg. This subject died on day 1 for a myocardial infarction.
- Subject # 687-411 (randomized to Natrecor fixed Dose) died of cardiac arrest following randomization and before study drug was started on day 1.
- Subject # 585-501 (randomized to placebo followed by Natrecor fixed dose) withdrew consent when he was informed that he was sustaining a myocardial infarction
- Subject # 369-510 (randomized to placebo followed by Natrecor fixed dose) had improvement in clinical symptoms before the start of infusion.

• Subject # 357-505 (randomized to Natrecor fixed dose) had improvement in clinical symptoms before the start of infusion.

• Subject # 540-406 (randomized to nitroglycerin); • Subject # (554-424 (randomized to nitroglycerin) • # 572-415 (randomized to placebo followed by Natrecor fixed dose) and • Subject #647-401 (randomized to Natrecor adjustable dose) all discontinued before infusion because the baseline PCWP was less than 20 mm Hg.

Among those who entered the study and received infusions two subjects, one subject (catheterized, Natrecor adjustable dose) and one subject (not catheterized subject randomized to placebo followed by Natrecor fixed dose) had no baseline dyspnea information available.

Two subject # 357-502 and #369-518, randomized to Natrecor fixed dose (not catheterized) discontinued due to adverse events during the three hour placebo-controlled period.

There were a total of 487 subjects who completed the three-hour placebo-controlled infusion period. There were four subjects who did not have available hemodynamic (one subject randomized to nitroglycerine and three subjects randomized to Natrecor fixed does). There were, therefore, a total of 246 subjects who were catheterized and had hemodynamic data available at the 3-hour time point. There was one catheterized subject randomized to Natrecor adjustable dose who had no dyspnea data available. There were 486 subjects who had symptom data available at the 3-hour time point.

A total of 487 continued into the 24-hour infusion period. A total of 30 subjects discontinued prior to the completion of 24-hours of infusion. Eighteen of these subjects discontinued due to adverse events, four subjects withdrew consent, four had worsening of their status or had an inadequate clinical response and 4 subjects had improvement of their status obviating the need for longer infusion.

The number of subjects who had available baseline and 24-hour hemodynamic and dyspnea data were 227 and 481, respectively.

Table 5. Subject accounting

	Catheterized					Not Catheterized				Total
	NAT Adjust. Dose	NTG	NAT Fixed Dose	PBO:NAT Fixed Dose	PBO:NTG	NTG	PBO:NAT Fixed Dose	PBO:NTG	Nat Fixed Dose	
Randomized (Total = 498)	63	62	63	31	32	83	41	41	82	498
Received infusions (Total=489)	62	60	62	30	32	83	39	41	80	489
Missing data at baseline	1	0	0	0	0	0	1	0	0	2
Missing baseline hemodynamics	0	0	0	0	0	N/A	N/A	N/A	N/A	0
Missing dyspnea	1	0	0	0	0	0	1	0	0	2
Missing both	0	0	0	0	0	N/A	N/A	N/A	N/A	0
Did not receive drug (n=9)	1	2	1	1	0	0	2	0	2	9
Died	0	0	1	0	0	0	0	0	1	2
PCWP < 20 mm Hg	1	2	0	1	0	N/A	N/A	N/A	N/A	4
Ongoing MI	0	0	0	0	0	0	1*	0	0	0
Symptoms improved	0	0	1	0	0	0	1	0	1	2
Withdrew consent	0	0	0	0	0		1*	0	0	1
Completed 3-hour infusion data available	62	60	62	30	32	83	39	41	78	487
Completed 3-hour infusion missing data	1	1	3	0	0	0	0	0	0	5
Missing hemodynamics	0	1	3	0	0	N/A	N/A	N/A	NA	4
Missing dyspnea	1	0	0	0	0	0	0	0	0	1
Missing both	0	0	0	0	0	0	0	0	0	0
Did not complete 3-hour infusion	0	0	0	0	0	0	0	0	2	2
Died	0	0	0	0	0	0	0	0	0	0
ADR	0	0	0	0	0	0	0	0	2	2
Withdrew consent	0	0	0	0	0	0	0	0	0	0
Worsened or inadequate clinical response	0	0	0	0	0	0	0	0	0	0
Improved	0	0	0	0	0	0	0	0	0	0
Entered 24 hour infusion	62	60	62	30	32	83	39	41	78	487
Completed 24-hour infusion	57	56	58	28	30	79	38	39	72	457
Did not complete 24-hour infusion	5	4	4	2	2	4	1	2	6	30
Died	0	0	0	0	0	0	0	0	0	0
ADR	2	2	2	1	1	3	1	1	5	18
Withdrew Consent	1	1	0	0	0	0	0	1	1	4
Worsened or inadequate clinical response	0	1	2	0	0	1	0	0	0	4
Improved	2	0	0	1	1	0	0	0	0	4

*One subject withdrew consent when he found out that he was undergoing a myocardial infarction.

Since a Swan-Ganz catheter was optional for this study, the reason for catheterization is shown in Table 6. Most subjects were catheterized because hemodynamic values at baseline were uncertain. Catheterization was frequently used to optimize out subject medication. Table 6 below contains both the primary reason and any contributory reason for the insertion of the catheter.

Table 6. Reasons for catheterization (prim= primary reason)

	Nat Adj Dose (n= 62)		NTG (n= 60)		Nat Fixed Dose (n=62)		PBO:Nat Fixed dose (n=30)		PBO: NTG (n=32)	
	Prim	Any	Prim	Any	Prim	Any	Prim	Any	Prim	Any
Low or unstable BP	1 (2%)	7 (11%)	0	4 (7%)	1 (2%)	5 (8%)	0	0	0	3 (9%)
Uncertain hemodynamics	34 (55%)	54 (87%)	32(53%)	46 (77%)	30 (48%)	56 (90%)	13 (43%)	23(77%)	17(53%)	25(78%)
Low cardiac output suspected	10 (16%)	36 (58%)	12 (20%)	29 (48%)	12 (19%)	37 (60%)	7 (23%)	15(50%)	6 (19%)	14(44%)
Potential Transplant Candidate	2 (3%)	7 (11%)	1 (2%)	7 (12%)	6 (10%)	13 (21%)	2 (7%)	10(33%)	1(3%)	4 (13%)
Significant Renal Dysfunction	1 (2%)	13(21%)	1 (2%)	8 (13%)	0	12 (19%)	1 (3%)	7 (23%)	0	0
Significant Metabolic Abnormality	0	2 (3%)	0	2 (3%)	0	0	0	2 (7%)	0	0
To optimize outsubject Medication	13 (21%)	29 (47%)	11 (18%)	27 (45%)	10 (16%)	26 (42%)	5 (17%)	12 (40%)	7 (22%)	16(50%)
Other	1 (2%)	3 (5%)	3 (5%)	5 (8%)	3 (5%)	6 (10%)	2 (7%)	3 (10%)	1 (3%)	1(3%)

Demographics: The baseline demographics of those enrolled are shown in Table 7

Table 7. Demographics at baseline (Sponsors Tables 3)

	Catheterized			Not-Catheterized		
	NTG (n=60)	Natrecor Fixed ± Adjust (n=124)	PBO (n=62)	NTG (n=83)	Natrecor (n=80)	PBO (n=80)
Age, years mean ± SD	59 ± 15	63 ± 12	59 ± 16	62 ± 14	62 ± 13	65 + 15
Ethnicity						
Black	17 (28%)	30 (24%)	14 (23%)	18 (22%)	20(25%)	20 (25%)
Caucasian	34 (57%)	76 (61%)	39 (63%)	51 (61%)	42 (53%)	44 (55%)
Other	9 (15%)	18 (15%)	9 (14%)	14 (17%)	18 (22%)	16 (20%)
Gender						
Male	43 (72%)	95 (77%)	47 (76%)	43 (52%)	53 (66%)	56 (70%)
Female	17 (28%)	29 (23%)	15 (24%)	40 (48%)	27 (34%)	24 (30%)
Weight Kg mean ± SD	85 ± 22	81 ± 19	86 ± 23	82 ± 23	85 ± 22	83 + 24
Etiology of Cardiomyopathy						
Ischemic	27 (48%)	73 (63%)	34 (59%)	34 (42%)	29 (39%)	44 (59%)
Idiopathic, dilated	15 (27%)	24 (21%)	14 (24%)	24 (32%)	21 (28%)	15 (20%)
Hypertensive	7 (13%)	5 (4%)	3 (5%)	8 (11%)	13 (17%)	9 (12%)
Alcohol	1 (2%)	3 (3%)	1 (2%)	0	1 (1%)	1 (1%)
Valvular/Rheumatic	3 (5%)	8 (7%)	4 (7%)	4 (5%)	4 (5%)	2 (3%)
Diabetic	0	0	0	0	2 (3%)	0
Drug	0	0	0	0	1 (1%)	0
Postpartum	0	0	0	1 (1%)	0	0
Viral Myocarditis	2 (4%)	0	1 (2%)	4 (5%)	0	0
Thyrotoxicosis	0	0	0	0	0	0
Other	1 (2%)	1 (1%)	1 (2%)	2 (3%)	0	0
Unknown	0	2 (2%)	0	1(1%)	4 (5%)	3 (4%)
Missing	4 (7%)	8 (6%)	4 (6%)	7 (8%)	5 (6%)	6 (7%)
Hist. Coronary Artery Disease	38 (63%)	91 (73%)	39 (63%)	52 (63%)	43 (54%)	56 (70%)
AICD present	14 (23%)	42 (34%)	18 (29%)	17 (20%)	13 (16%)	18 (23%)
Hist of Cardiac Revascularization	18 (30%)	58 (47%)	25 (40%)	24(29%)	23 (29%)	34 (43%)
Hist Previous MI	28 (47%)	67 (54%)	28 (45%)	31 (37%)	29 (36%)	42 (53%)
MI < 7 days						
Q-wave	0	1 (1%)	2 (3%)	1 (1%)	2 (3%)	2 (3 %)
Non-Q-wave	5 (8%)	3 (2%)	1 (2%)	4 (5%)	1 (1%)	4 (5%)
Acute Coronary Syndr < 7 days	6 (10%)	10 (8 %)	4 (6%)	14 (17%)	10 (13%)	17 (21%)
<24 hours	1 (2%)	5 (4%)	1 (2%)	8 (10%)	5 (6%)	8 (10%)

The population that was enrolled was reasonably well balanced across treatment groups. Ischemic cardiomyopathy was the most common etiology of heart failure. Coronary artery disease was common and observed in 54-73% of those enrolled. A small fraction of those enrolled had a recent MI (< 7 days, 3-8%). 10-21% had an acute coronary syndrome event within the week prior to the study. There was no overwhelming difference in comparing the catheterized to not-catheterized subjects. Approximately 15-30% of those enrolled had an AICD in place.

The signs and symptoms of CHF are shown in Table 8. Rales and peripheral edema were the most common symptoms and were present in approximately 64-84% of those enrolled. Ejection fraction among those catheterized were somewhat less than that of the not-catheterized subjects. Subjects were largely class III and IV subjects.

Table 8. Symptoms and Severity of CHF at baseline

	Catheterized			Not Catheterized		
	NTG (n=60)	Natrecor Fixed ± Adjust (n=124)	PBO (n=62)	NTG (n=83)	Natrecor (n=80)	PBO (n=80)
Rales present (%)	37 (62%)	92 (74%)	44 (71%)	69 (83%)	55 (69%)	62 (78%)
S3 present (%)	35 (58%)	69 (56%)	40 (63%)	47 (57%)	51 (64%)	48 (60%)
S4 present (%)	15 (25%	24 (20%)	10 (16%)	22 (27%	21 (26%)	13 (16%)
Murmurs present (%)	40 (67%)	79 (64%)	37 (61%)	44 (54%)	42 (53%)	49 (61%)
Hepatomegaly present (%)	22 (39%)	52 (44%)	24 (43%)	24 (31%)	26 (34%)	28 (38%)
Pedal Edema present (%)	38 (63%)	78 (63%)	44 (71%)	65 (78%)	65 (81%)	66 (83%)
Ejection Fraction mean ± SD*	24 ± 13	24 ± 12	26 ± 13	27 ± 16	30 ± 14	30 ± 15
EF>40%	6 (11%)	11 (9%)	7 (12%)	13 (18%)	15 (21%)	13 (19%)
Previous NYHA Class (prior to admission)						
I						
II	4 (7%)	10 (8%)	5 (8%)	9 (11%)	7 (9%)	7 (9%)
III	10 (17%)	10 (8%)	2 (3%)	8 (10%)	3 (4%)	5 (6%)
IV	28 (47%)	50 (40%)	24 (39%)	29 (35%)	39 (49 %)	35 (44%)
	18 (30%)	54 (44%)	31 (50%)	37 (45%)	31 (39%)	33 (41%)

* Last available measurement, not necessarily associated with this study.

Medications that were taken within six hours of the start of the infusion are shown in Table 9. Inotropic support (PDE III inhibitors, dopamine or dobutamine) were administered to approximately 20% of those enrolled within 6-hours of entry into the study. The exception was the NTG (not catheterized) group in which only 7% received some form of pressor. IV after-load reducers (IV nitroglycerine or nitroprusside) were administered to approximately 5% of those enrolled. IV diuretics were administered to 35% of those enrolled.

Table 9. Medications taken within 6 hours prior to the start of study drug.

	Catheterized			Not Catheterized		
	NTG (n=60)	Natrecor Fixed ± Adjust (n=124)	PBO (n=62)	NTG (n=83)	Natrecor (n=80)	PBO (n=80)
Diuretics	25(42%)	43 (35 %)	23 (37 %)	50 (60 %)	45 (56 %)	41 (51 %)
IV diuretics	15 (25%)	34 (27 %)	16 (26 %)	34 (41 %)	27 (34 %)	31 (39 %)
Oral diuretics	13 (22%)	18 (15 %)	11 (18 %)	22 (27 %)	24 (30 %)	17 (21 %)
Digoxin	13 (22%)	26 (21 %)	11 (18 %)	24 (29 %)	27 (34 %)	24 (30 %)
IV Digoxin	0	2 (2%)	0	0	0	1(1 %)
Aspirin	12 (20%)	26 (21 %)	11 (18 %)	23 (28 %)	19 (24 %)	27 (34 %)
ACE inhibitors	8 (13%)	26 (21 %)	12 (19 %)	21 (25 %)	25 (31 %)	27 (34 %)
Non-IV Nitrates	7 (12 %)	23 19 %)	10 (16 %)	25 (30 %)	19 (24 %)	18 (23 %)
IV Nitroglycerine	0	3 (2 %)	3 (5 %)	2 (2 %)	3 (4 %)	1 (1 %)
Beta Blockers	5 (8 %)	16 (13 %)	1 (2 %)	17 (20 %)	12 (15 %)	12 (15 %)
IV Beta blockers	0	1 (1 %)	0	0	0	1 (1 %)
Anticoagulants:						
Warfarin	1 (2 %)	4 (3 %)	1 (2 %)	2 (2 %)	2 (3 %)	3 (4 %)
Heparin	3 (5%)	10 (8%)	7 (11%)	6 (7 %)	9 (11 %)	10(13 %)
Statins	1 (2 %)	3 (2 %)	2 (3 %)	3 (4 %)	1 (1 %)	2 (3 %)
Class III antiarrhythmics	1(2 %)	16 (13 %)	3 (5 %)	4 (5 %)	7 (9 %)	6 (8 %)
Calcium Channel Blockers	2 (3 %)	8 (6%)	2 (3 %)	4 (5 %)	8 (10 %)	9 (11 %)
Angiotensin II Blockers	2 (3 %)	0	1 (2 %)	5 (6 %)	4 (5 %)	1 (1 %)
Hydralazine	3 (5 %)	9 (7 %)	1 (2 %)	3 (4 %)	4 (5 %)	3 (4 %)
Other antihypertensives	0	0	0	1 (1 %)	1 (1 %)	0
Other antiarrhythmics	0	2 (2 %)	0	2 (2 %)	0	0
IIb/IIIa inhibitors	4 (7 %)	2 (2 %)	1 (2 %)	2 (2 %)	2 (3 %)	4 (5 %)
Dobutamine	9 (15 %)	19 (15%)	14 (23 %)	5 (6 %)	16 (20 %)	12 (15 %)
PDE inhibitors	0	2 (2 %)	2 (3 %)	1 (1 %)	0	1(1%)
Dopamine	2 (3 %)	13 (10 %)	1 (2 %)	0	4 (5%)	5 (6 %)
Nitroprusside	0	1 (1 %)	1 (2 %)	1 (1 %)	1 (1 %)	1 (1 %)
Pressors	0	0	0	0	0	0

The medications taken within 24 hours of starting the study drug infusion is shown in Table 10. The pattern of medication use over this longer period prior to entering the study show that 20-25% were treated with intravenous pressors, and approximately 5% with after load reducers. (The NTG not-catheterized group was unusual in the low use of dobutamine =5%). Intravenous diuretics were administered to approximately 45-50% of those enrolled.

Table 10. Selected medications taken within 24 hours prior to the start of study drug.

	Catheterized			Not Catheterized		
	NTG (n=60)	Natrecor Fixed ± Adjust (n=124)	PBO (n=62)	NTG (n=83)	Natrecor (n=80)	PBO (n=80)
Diuretics	45 (75%)	85 (69 %)	47 (76 %)	73 (88 %)	7145 (89 %)	73 (91 %)
IV diuretics	31 (52%)	64 (52 %)	30 (48 %)	57 (69 %)	51 (64 %)	57 (71 %)
Oral diuretics	31 (52%)	42 (34 %)	25 (40 %)	37 (45 %)	40 (50 %)	31 (39 %)
Digoxin	24 (40%)	62 (50 %)	29 (47 %)	45 (54 %)	41 (51%)	38 (48 %)
IV Digoxin	0	5 (4%)	1(2%)	1 (1%)	1 (1%)	2(3 %)
Aspirin	25 (42%)	50 (40 %)	20 (32 %)	42 (51 %)	33 (41 %)	35 (44 %)
ACE inhibitors	19 (32%)	62 (50 %)	29 (47 %)	44 (53 %)	45 (56 %)	42 (53 %)
Non-IV Nitrates	18 (30 %)	43 (35 %)	16 (26 %)	37 (45 %)	31 (39 %)	31 (39 %)
IV Nitroglycerine	0	6 (5 %)	3 (5 %)	6 (7 %)	3 (4 %)	3 (4 %)
Beta Blockers	17 (28 %)	30 (24 %)	11 (18 %)	25 (30 %)	20 (25 %)	20 (25 %)
IV Beta blockers	0	2 (2 %)	0	1 (1%)	3 (4%)	3 (4 %)
Anticoagulants:						
Warfarin	6 (10 %)	11 (9 %)	2 (3 %)	15 (18 %)	13 (16 %)	10 (13 %)
Heparin	5 (8%)	15 (12%)	7 (11%)	9 (11 %)	11 (14 %)	13 (16 %)
Angiotensin II Blockers	2 (3 %)	3 (2%)	5 (8 %)	8 (10 %)	6 (8 %)	4 (5 %)
Dobutamine	10 (17 %)	21 (17%)	14 (23 %)	5 (6 %)	18 (23 %)	12 (15 %)
PDE inhibitors	0	4 (3 %)	4 (6 %)	1 (1 %)	0	1 (1%)
Dopamine	2 (3 %)	13 (10 %)	1 (2 %)	0	5 (6%)	5 (6 %)
Nitropursside	0	1 (1 %)	1 (2 %)	1 (1 %)	1 (1 %)	1 (1 %)
Pressors	0	0	0	0	0	0

Taken as a whole, approximately 20-35% of those enrolled was treated with pressors or afterload reducers. Intravenous diuretics were used in approximately 50% of those enrolled. Afterload reducers were administered to a small fraction of those enrolled.

Blinding:

There were several situations where unblinding of treatments occurred during the study but distant in time from the time the subject was infused.

- The investigator of study site # 554 was asked to sign treatment logs. The investigator signed the logs but claims to not have reviewed the treatment assignments. At the time of the unblinding 54 of the 56 subjects whose blinding was compromised were past 14 days and 46/56 subjects were past 30 days follow-up.
- A Scios CRA was unblinded to the list of NTG that was out of specifications. The list included the numbers of eight subjects exposed to the NTG shipment.
- A Scios monitor was inadvertently unblinded to two subject's treatment while on a monitoring visit.
- A Scios monitor was inadvertently unblinded to a PBO/NTG subject during a conversation with a pharmacist.

Dose of study medications:

With respect to the study medication, the sponsor tabulates several subjects whose dosing violated the stipulated protocol. The specifics are tabulated below.

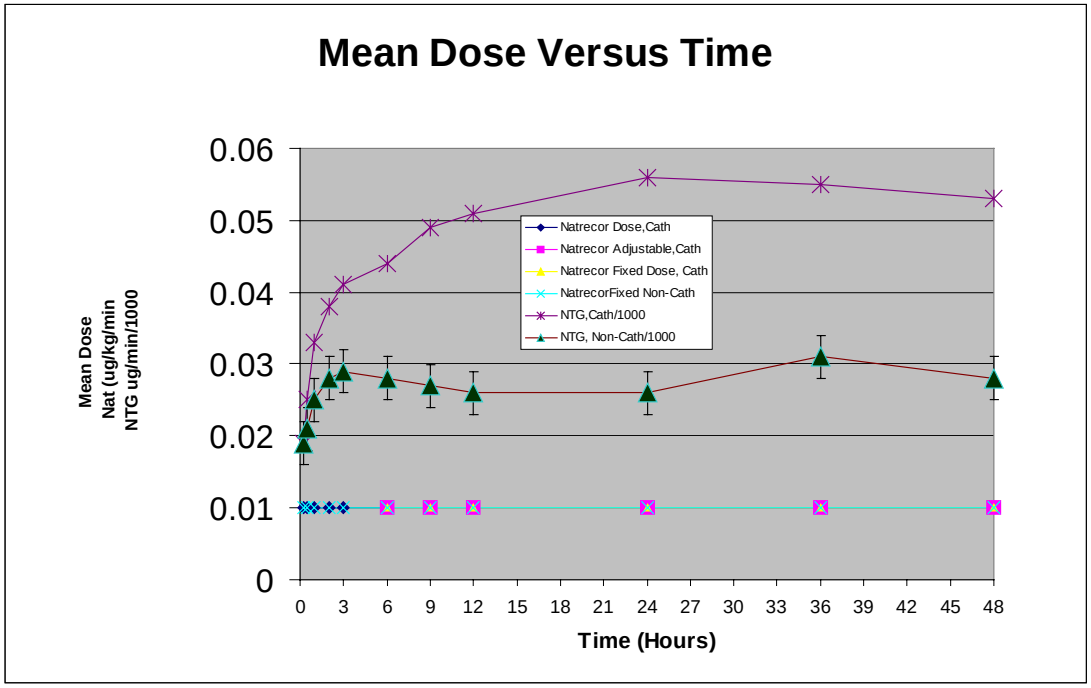
Table 11. Study Drug Dosing Deviations

	NTG	NAT	ALL
Placebo-controlled Period			
Incorrect initial NAT/PBO bolus volume	6	9	15
Incorrect NAT/PBO Infusion flow rate	10	16	26
Active-controlled period			
No crossover NAT/PBO bolus administration	8	7	15
Incorrect crossover NAT/PBO bolus volume > 10%	1	2	3
Incorrect crossover NAT/PBO infusion flow rate >10%	2	4	6
Stop time of infusion > 15 minutes different between two infusions	5	3	8

- # 671-402 this subject had a dose increase to 0.03 ug/kg/min faster than allowed by the protocol.
- # 666-503 received the medication for subject #666-504 who was randomized to the same medication (fixed dose Natrecor).
- # 638-502 (NTG) the infusion line infiltrated at the beginning of the bolus. The remainder of the bolus was administered five hours later. The time of the second bolus was considered as time 0. The subject was not catheterized and the measurements effect only dyspnea and global assessments.
- # 543-405 (PBO/NTG) did not cross over due to PCWP < 12 mm Hg
- # 357-502 and #369518 (both NAT fixed dose) discontinued during the 3-hour phase due to asymptomatic hypotension
- # 636-502 (NAT fixed dose) continued on infusion for 161 days.

The dose of medication in the individual treatment groups is shown in Figure 2. The mean dose of Natrecor, either among those catheterized or not catheterized was the same (0.01 ug/kg/min) during the 3-hour placebo-controlled and 24-hour blinded infusion periods. The dose of NTG increased over time. The increase in dose among those catheterized was faster than among those not catheterized.

Figure 2 Mean dose versus time of Natrecor versus Nitroglycerin



The distribution of subjects who were treated with a specific dose range is shown in Figure 3 for Natrecor- and Figure 4 for the NTG-treated subjects. Among those treated with the fixed dose Natrecor doses (both catheterized and not catheterized), few subjects received doses higher than the 0.01 ug/kg/min dose. Among those treated with the adjustable Natrecor dose, approximately 40% of the subjects at one time received doses centered around 0.015 ug/kg/min. Approximately 20% of those treated with Natrecor had doses reduced (centered around 0.005 ug/kg/min).

The specific reasons for the dosing changes are shown in Table 12. This table includes the placebo crossover subjects into their new treatment regimen. Among those catheterized or not catheterized, many more nitroglycerin subjects had modifications of their dose than did Natrecor subjects. The adjustable dose Natrecor (catheterized) had more dosing changes than fixed dose Natrecor (catheterized) subjects. Subjects could have more than one increase or decrease and the number of increases and decrease in dose are also shown in Table 12. The reasons for the dose reduction are also shown in table 12. Only approximately 10% of those treated either with NTG or Natrecor fixed or adjustable doses had their doses reduced or interrupted due to adverse events. A large proportion of those whose dose was reduced was a consequence of clinical improvement (clinical effect).

Figure 3

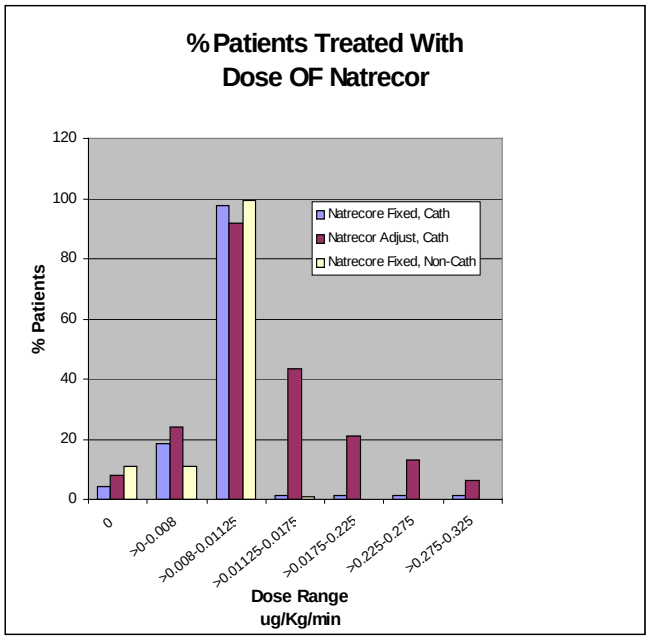


Figure 4

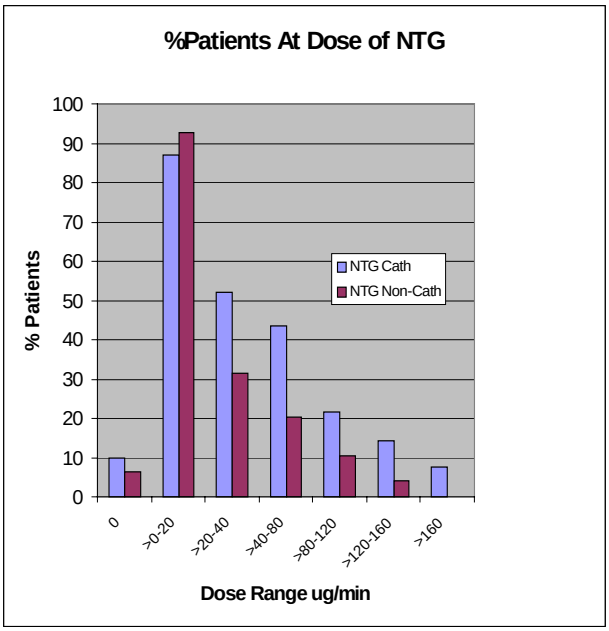


Table 12 reason for dose change

	Catheterized			Non-Catheterized		
	Natrecor Fixed* (n=92)	Natrecor Adj (N=62)	NTG* (n=92)	Natrecor Fixed (n=119)	NTG* (n=124)	
Number remaining on initial dose (% Subjects)	74 (80%)	25 (40%)	29 (32%)	100 (84%)	76 (61%)	
Type of dose modification # Pts (%)	18 (20%)	37 (60%)	62 (67%)	19 (16%)	48 (39%)	
Dose Increase	4 (4%)	24 (39%)	57 (62%)	2 (2%)	38 (31%)	
Dose Reduction	17 (18%)	22 (35%)	30 (33%)	13 (11%)	23 (19%)	
Dose Interruption	1(1%)	3 (5%)	4 (4%)	5 (4%)	7 (6%)	
Type of dose modification (# events)						
Dose Increase	7	52	291	2	132	
Dose Reduction	29	37	50	14	47	
Dose Interruption	1	3	4	5	9	
Reason for Dose Reduction/Interruptions (# Pts)	18 (22%)	25 (40%)	33 (37%)	18 (15%)	27 (25%)	
To clinical effect	7 (8%)	15 (24%)	17 (20%)	2 (2%)	14 (12%)	
Adverse event	9 (10%)	6 (11%)	10 (13%)	14 (12%)	9 (9%)	
Other/NA	2 (2%)	4 (5%)	6 (8%)	2 (2%)	4 (3%)	
* Consists of randomized plus placebo crossovers. Sponsor's table 40.2 –40.3						

Concomitant medications during the three-hour infusion period are shown in Table 13. During the 3-hour placebo controlled period, approximately 15% (4-23%) of those enrolled were treated with concomitant dobutamine that was ongoing at baseline. Approximately 5% (0-9%) of the subjects enrolled were treated with dopamine at the time of entry and continued while on study drug. One Natrecor fixed dose and one placebo catheterized subjects had dobutamine newly added during this period. One Natrecor (not catheterized subject had dopamine newly added during the infusion.

Table 13 Selected medications taken during 3-hour PBO controlled period

	Catheterized			Not Catheterized		
	NTG (n=60)	Natrecor Fixed ± Adjust (n=124)	PBO (n=62)	NTG (n=83)	Natrecor (n=80)	PBO (n=80)
Diuretics	15 (25%)	26 (21 %)	18 (29 %)	12 (14 %)	17 (21 %)	11 (14 %)
IV diuretics	9 (15%)	19 (15 %)	12 (19 %)	10 (12 %)	8 (10 %)	7 (9 %)
Oral diuretics	8 (13%)	9 (7 %)	7 (11 %)	3 (4 %)	6 (8 %)	6 (8 %)
Digoxin	6 (10%)	9 (7 %)	9 (15 %)	5 (6 %)	6 (8%)	8 (10 %)
IV Digoxin	1 (2%)	0	0	1 (1%)	1 (1%)	0
ACE inhibitors	8 (13%)	14(11 %)	11 (13 %)	11 (13 %)	11 (14 %)	6 (8 %)
Non-IV Nitrates	3 (5 %)	10 (8 %)	11 (18 %)	9 (11 %)	9 (11 %)	9 (11 %)
IV Nitroglycerine	0	0	0	0	0	0
Beta Blockers	4 (7 %)	11 (9 %)	3 (5 %)	3 (4 %)	5 (6 %)	4 (5 %)
IV Beta blockers	1(2%)	0	0	0	0	**0**
Angiotensin II Blockers	1 (2 %)	3 (2%)	1 (2 %)	0	1 (1 %)	2 (3 %)
Dobutamine	8 (13%)	19 (15%)	15 (24%)	3 (4 %)	15 (19 %)	11 (14 %)
Continued at Baseline	8 (13%)	18 (15%)	14 (23%)	3 (4%)	15 (19%)	11 (14%)
New Administration	0	1 (%)	1 (2%)	0	0	0
PDE inhibitors	0	0	0	0	0	0
Dopamine	2 (3 %)	11 (9 %)	1 (2 %)	0	5 (6%)	4 (5 %)
Continued at Baseline	2 (3%)	11 (9%)	1 (2%)	0	4 (5%)	4 (5%)
New Administration	0	0	0	0	1 (1%)	0
nitroprusside	0	0	0	0	0	1 (1 %)
Pressors	0	0	0	0	0	0

Primary Efficacy End points

1. *Hemodynamics PCWP at 3 hours:* This parameter was assessed only among those catheterized.

Quality of data: There were 3 subjects who had missing values for PCWP. The three subjects were all in the Natrecor (Fixed dose) regimen. The subjects (# 369417, #540408 and 678404) all completed the three-hour infusion with other hemodynamic data available (notably cardiac output) that showed no deterioration in cardiac function. Censoring of these subjects, therefore, is unlikely to bias the results.

This analysis of interest was the change from baseline at three hours of the infusion. Baseline measurements were to demonstrate stability of the PCWP measurement. Two values of PCWP at baseline were to not differ by more than 15% (of the higher or lower value?) were to be collected within 20 minutes of the start of the infusion and within 5-15 minutes of each other. The last of these values was to serve as baseline.

There were, however, many subjects whose values violated these prespecified criteria for baseline measurement. These deviations included less than two baseline measurements (N=7); at least one of the baseline measurements > 20 minutes before the start of the infusion (N=83); baseline measurements after the start of the infusion (N=9); duplicate measurements outside the 5-15 minute regimen (N=6). These deviations were distributed across all treatments and are not likely to bias the results.

The protocol proposed to maintain a firewall between the assessment of hemodynamics and unblinding of treatment. This unblinding (placebo versus active) was only to take place after the hemodynamics was completed. A log of the time at which the treatment was unblinded was kept. There, however, was no way to guarantee that these values were committed to the CRFs before the unblinding occurred. There were, in addition, several subjects for whom the time of symptom assessment occurred after the time of hemodynamics (the fraction on nitroglycerin: Natrecor: PBO were 1/60: 14/124: 13/62 patients, respectively). Consequently some fraction of patients could have had known hemodynamics at the time symptoms were assessed.

The sponsor's results for wedge pressures are shown below. The FDA's analysis is essentially the same.

Table 14 Pivotal wedge pressure assessment (per sponsor)

	Nitroglycerin (n-60)	Pooled Natrecor (n=124)	Placebo (n=62)
Baseline	28.0 + 5.7	27.7 + 7.0	27.7 + 5.5
3-hour	24.2 + 6.2	21.9 + 7.4	25.7 + 6.6
Mean Change from Baseline Mean + SD	-3.8 + 5.3	-5.8 + 6.5	-2.0 + 4.2
Least Square Mean + SE	-3.8 + 0.7	-5.8 + 0.5	-2.0 + 0.7
p-value versus Placebo	0.087	<0.001	
p-value Natrecor versus Nitroglycerine		0.027	

Three Hour Dyspnea Evaluation:

This metric defines the nature of the dyspnea at baseline as well as the degree of dyspnea at 24-hours. The ordinal descriptive categories consist of:

- At rest while sitting;
- At rest while lying flat or with one pillow;

- With minimal activity (such as talking eating or bathing);
- With walking short distances (such as to the bathroom);
- With walking distances greater than 50 feet;
- With walking up stairs or running;
- The subject did not have difficulty breathing.

At hours ¼, ½, 1, 2, 3, 6 and 24 the subject was asked to rate their change in discomfort from baseline. It is this metric which is part of the primary endpoint of the study.

It is unclear how the metric was finalized prior to unblinding placebo from active treatments.

Quality of the data: There was only one subject with no data (subject # 357-401 treated with adjustable dose Natrecor; catheterized). This subject apparently was confused and could not give cogent symptom responses. Subject # 554-503 (fixed dose, not catheterized) had no descriptive baseline assessment available but had the measurements of change in symptoms collected at the appropriate time. There were 49 subjects who had baseline symptoms assessed at times fairly distant (i.e. > 1 hour) prior to the start of the infusion. The longest pre-infusion assessment of baseline was > 4 hours. Three subjects had their baseline symptoms ascertained at a time point after the start of infusion but generally minutes of the start of infusion.

(Comment: Since the placebo group had a substantial symptomatic benefit, time itself affords some improvement in symptoms. The time from the start of the infusion for which the baseline symptoms were assessed could be important in the assessment of response. I do not have this analysis yet.).

Baseline Measurements: The specific description by the subject of their degree of dyspnea at baseline is shown in Table 15.

Table 15: Description of baseline degree of dyspnea.

	Catheterized					Not Catheterized				Total
	ANAT	FNAT	PLA:NAT	PLA:NTG	NTG	FNAT	PLA:NAT	PLA:NTG	NTG	
	N=62	N=62	N=30	N=32	N=61	N=80	N=40	N=40	N=83	489
At rest while sitting	28 (44%)	31 (50%)	9 (31%)	10 (31%)	29 (48%)	39 (48%)	18 (48%)	19 (48%)	38 (46%)	220(45%)
At rest while lying flat or with one pillow	21 (34%)	14 (23%)	16 (55%)	14 (44%)	20 (33%)	29 (36%)	11 (28%)	16 (40%)	37 (45%)	179(36%)
With minimal activity (such as talking, eating or bathing)	7 (11%)	14 (23%)	2 (7%)	4 (13%)	10 (16%)	7 (6%)	5 (6%)	5 (13%)	5 (6%)	60 (12%)
With walking short distances (such as to the bathroom)	2 (4%)	2 (3%)	2 (4%)	0	2 (6%)	2 (3%)	3 (3%)	0	3 (4%)	15 (3%)
With walking distances greater than 50 feet	3 (5%)	0	0	2 (6%)	0	1 (1%)	2 (3%)	0	0	8 (2%)
With walking up stairs or running	0	1 (2%)	0	2 (6%)	0	1 (1%)	0	0	0	4 (1%)
The subject had no difficulty with breathing	0	0	1 (1%)	0	0	0	0	0	0	1 (<1%)
Not assessed	1 (2%)	0	0	0	0	1(1%)	0	0	0	2 (<1%)

Of those enrolled, 45% had symptoms at rest another 36% had orthopnea. The other subjects enrolled (approximately 19%) had symptoms with mild or more rigorous activities. In reality this fraction of subjects did not adhere to the protocol requirement of dyspnea at rest. Two subjects did not have symptoms assessed at baseline. (Comment: the sponsor notes that symptom assessment was made at times distant to enrollment. At the time they entered the study the sponsor claims the patients all had dyspnea at rest).

The change from baseline is shown below. The p-values reflect the sponsor's analysis. The groups seem well balanced, except that there were fewer subjects who had symptoms at rest those catheterized subjects, who were randomized to placebo followed either by nitroglycerine or Natrecor. Two subjects had missing assessments at baseline. One of these subjects, however, had the symptoms change assessed so that this subject contributed to this analysis. One subject # 357-401 had no measurements taken and was censored from this analysis.

(Comment: Since baseline symptoms may have been different among the different groups, an analysis should be done with baseline symptom as covariate)

Table 16. Change in dyspnea

	NTG (n=143)	Natrecor (N=204)	Placebo (n=142)
3 hour Evaluation			
Markedly better (+3)	14 (12%)	34 (17%)	25 (18%)
Moderately better (+2)	50 (35%)	54 (27%)	24 (17%)
Minimally better (+1)	37 (26%)	64 (32%)	41 (29%)
No Change (0)	33 (23%)	45 (22%)	46 (32%)
Minimally Worse (-1)	5 (3%)	5 (2%)	6 (4 %)
Moderately worse (-2)	0 (0%)	1 (<1%)	0 (0%)
Markedly worse (-3)	1 (1%)	0 (0%)	0 (0%)
p-value compared to placebo	0.191	0.034	
p-value Natrecor compared to NTG		0.6	

The sponsor performed an alternate analysis (not the primary end point), assigning a numeric value for each change in symptoms as shown above that is +3 for markedly better, +2 for moderately better etc. The analysis then treated the resultant numbers as a continuous variable. This analysis is shown in Table 17:

Table 17. Analysis treating change in dyspnea as linear outcomes.

	Nitroglycerin (n=143)	Natrecor (N=204)	Placebo (n=142)
3-Hour mean (+ SD)	1.3 + 1.1	1.3 + 1.1	1.1 + 1.2
Least Square Mean + SE	1.2 + 0.1	1.3 + 0.1	1.1 + 0.1
p-Value versus placebo (2-way ANOVA)	0.285	0.050	
p-value Natrecor		0.414	

Other hemodynamic measurements till three hours:

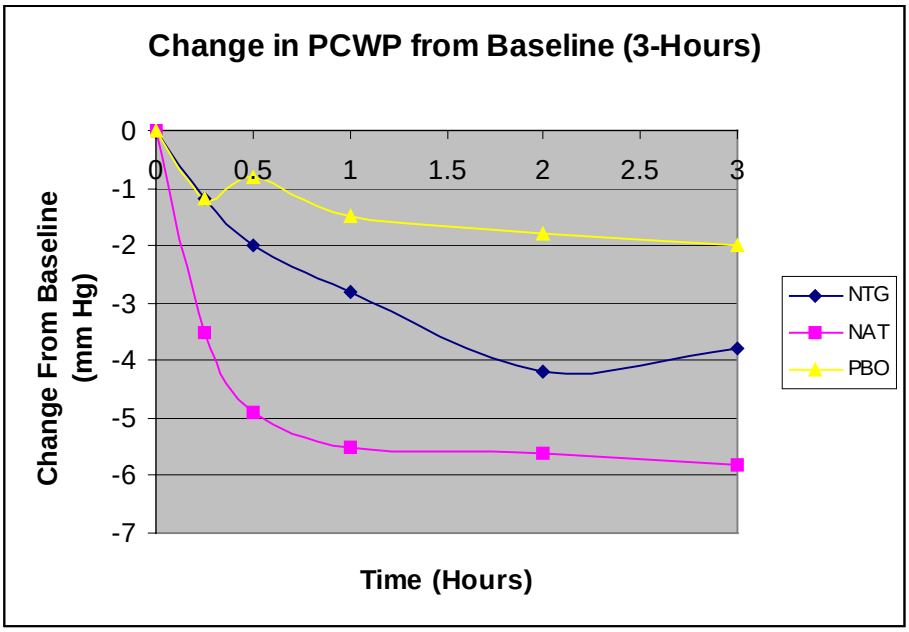
PCWP: The Natrecor adjustable dose and Natrecor fixed dose were pooled as pre-specified for this analysis. Hemodynamic measurements were only available for those with an indwelling catheter. The time course in shown in Table 18 and displayed as figure 5.

The effect on those treated with Natrecor shows a rapid drop in wedge pressure obvious even at 0.25 hours, with a steady effect observed between 1-3 hours the effect of Natrecor is fairly constant. For those treated NTG there is an increase in effect over time. The benefit of NTG did not occur till somewhat later than the effect on wedge pressure observed with NAT.

Table 18. Time course of PCWP

		NTG (n=60	Natrecor (N=124)	PBO (N=62)
Baseline	N = /Missing ( )	60 (0)	124 (0)	62 (0)
	Mean ± SD	28.0 ± 5.7	27.7 ± 7.0	27.7 ± 5.4
0.25 Hr	N= / missing in ( )	58 (2)	121 (3)	62 (0)
	Change from Baseline (LS mean ± SE)	-1.2 ± 0.6	-3.5 ± 0.4	-1.2 ± 0.6
	p-value versus NTG		0.002	0.98
	p-value versus NAT			0.001
0.5 Hr	N= / missing in ( )	58 (2)	122 (2)	62 (0)
	Change from Baseline (LS mean ± SE)	-2.0 ± 0.6	-4.9 ± 0.4	-0.8 ± 0.6
	p-value versus NTG		0.000	0.18
	p-value versus NAT			0.000
1 Hr	N= / missing in ( )	58 (2)	121 (3)	62 (0)
	Change from Baseline (LS mean ± SE)	-2.8 0.7	-5.5 0.5	-1.5 ± 0.7
	p-value versus NTG		0.002	0.2
	p-value versus NAT			0.000
2 Hrs	N= / missing in ( )	56 (4)	118 (6)	61 (1)
	Change from Baseline (LS mean ± SE)	-4.2 ± 0.8	-5.6 ± 0.5	-1.8 ±0.7
	p-value versus NTG		0.139	0.024
	p-value versus NAT			0.000
3 Hrs	N= / missing in ( )	59 (1)	121 (3)	62 (0)
	Change from Baseline (LS mean ± SE)	-3.8 ± 0.7	-5.8 ± 0.5	-2.0 ± 0.7
	p-value versus NTG		0.027	0.087
	p-value versus NAT			0.000

Figure 5



Other hemodynamic measurements during first three hours aside from PCWP: Other hemodynamic measurements that were collected during the first three hours are shown in Table 19. With respect to right atrial pressure, there was a statistically (nominal) decrease in the Natrecor group relative to the placebo group as early as one hour into the infusion. At 1 hour, the effect of Natrecor was also superior to NTG in RAP. At 3 hours there was no difference between treatments. The reason for the lack of difference may be a reflection of the escalating NG doses.

With respect to systemic vascular resistance, decrease in resistance by those treated with Natrecor relative to placebo at 1 hour but not at 3 hours.

Table 19: Right atrial pressures and systemic vascular resistance during the three hour placebo-controlled period.

		Right Atrial Pressure				Systemic Vascular Resistance		
		NTG (n=60	Natrecor (N=124)	PBO (N=62)		NTG (n=60	Natrecor (N=124)	PBO (N=62)
BL	N = /Missing ( )	59 (1)	118 (6)	60 (2)		57 (3)	117 (7)	57 (5)
	Mean ± SD	15.9 ± 6.8	14.7 ± 6.8	14.2 ± 7.0		1508.7 ±697	1441 ± 589	1384 ± 563
1 Hr	N= / missing in ( )	58 (2)	120 (4)	60 (2)		57 (3)	118 (6)	59 (3)
	Change from Baseline (LS mean ± SE)	-1.0 ± 0.6	-2.6 ± 0.4	-0.2 ± 0.5		-136 ± 63	-236 ± 44	-8 ± 62
	p-value versus NTG		0.014	0.31			0.19	0.149
	p-value versus NAT			0.000				0.003
3 Hr	N= / missing in ( )	58 (2)	119 (5)	60 (2)		56 (4)	117 (7)	57 (5)
	Change from Baseline (LS mean ± SE)	-2.6 ± 0.6	-3.1 ± 0.4	0.0 ± 0.6		-105 ± 62	-144 ± 43	-44 ± 62
	p-value versus NTG		0.42	0.001			0.598	0.492
	p-value versus NAT			0.000				0.186

The relative effect of the treatments on cardiac index and pulmonary vascular resistance are shown in Table 20. Relative to placebo, Natrecor increases cardiac index (~19 % different) at the 1 hour time point. At the 3-hour time point there was an approximately 5% increase in cardiac index over placebo. At the 3-hour point, there was no difference relative to placebo. At the 1-hour time point, the effect of Natrecor was statistically (nominal) greater than that of NTG, there was no difference at 3 hours.

Natrecor decreased pulmonary vascular resistance, relative to placebo at both the 1 and 3 hour time points. There was no difference between Natrecor and NTG at either of these time points.

Table 20 Baseline and change from baseline for cardiac index and pulmonary vascular resistance.

		Cardiac Index (L/min/M2)				Pulmonary Vascular Resistance		
		NTG (n=60	Natrecor (N=124)	PBO (N=62)		NTG (n=60	Natrecor (N=124)	PBO (N=62)
BL	N = /Missing ( )	58 (2)	119 (5)	59 (3)		54 (6)	102 (22)	54 (8)
	Mean ± SD	2.1 ± 0.8	2.2 ± 0.7	2.2 ± 0.7		271 ±178	250 ± 168	236 ± 173
1 Hr	N= / missing in ( )	57 (3)	120 (4)	60 (2)		51 (9)	106 (18)	57 (3)
	Change from Baseline (LS mean ± SE)	0.1 ± 0.07	0.3 ± 0.05	-0.1 ± 0.07		-38 ± 17	-27 ± 12	+28 ± 16
	p-value versus NTG		0.008	0.08			0.6	0.004
	p-value versus NAT			0.000				0.006
3 Hr	N= / missing in ( )	56 (4)	120 (4)	58 (4)		51 (9)	103 (21)	55 (7)
	Change from Baseline (LS mean ± SE)	0.2 ± 0.07	0.1 ± 0.05	-0.0 ± 0.07		-18 ± 16	-21 ± 12	21 ± 16
	p-value versus NTG		0.79	0.09			0.91	0.082
	p-value versus NAT			0.09				0.037

The effect on mean pulmonary artery pressure is shown in Table 21. There was a decrease in mean pulmonary artery pressure of Natrecor relative to placebo at 1 and 3 hours. There was also a decrease in mean pulmonary artery pressure of Nat relative to placebo at 1 and 3 hours.

Table 21: Baseline and change from baseline for mean pulmonary artery pressures

		Mean Pulmonary Artery Pressure			
		NTG (n=60	Natrecor (N=124)	PBO (N=62)	
BL	N = /Missing ( )	60 (0)	122 (2)	62 (0)	
	Mean ± SD	38.9 ± 8.2	38.3 ± 8.6	39.2 ± 7.7	
1 Hr	N= / missing in ( )	59 (1)	124 (0)	62 (0)	
	Change from Baseline (LS mean ± SE)	-2.3 ± 0.8	-4.4 ± 0.5	-0.5 ± 0.8	
	p-value versus NTG		0.03	0.09	
	p-value versus NAT			0.000	
3 Hrs	N= / missing in ( )	59 (1)	124 (0)	62 (0)	
	Change from Baseline (LS mean ± SE)	-2.5 ± 0.8	-5.4 ± 0.6	-1.1 ± 0.8	
	p-value versus NTG		0.005	0.22	
	p-value versus NAT			0.000	

Symptoms up to three hours: The change in subject's symptoms over the initial 3 hours are shown in Table 22. The only significant value occurred at the three-hour time point in comparing the Natrecor treated subjects to placebo. There were no credible differences aside from the placebo-Natrecor comparison at three hours. A graphical representation of dyspnea benefit is shown in Figure 6.

Table 22: Time course of patient's dyspnea symptoms over the placebo-controlled period.

	0.25 Hours			0.5 Hours			1 Hour			2 Hour			3 Hour		
	NTG N=143	NAT N=204	PBO N=142	NTG N=143	NAT N=204	PBO N=142	NTG N=143	NAT N=204	PBO N=142	NTG N=143	NAT N=204	PBO N=142	NTG N=143	NAT N=214	PBO N=142
Markedly better	6 (4%)	16 (8%)	9 (6%)	9 (6%)	18 (9%)	11 (8%)	13 (9 %)	23 (11%)	13 (9%)	13 (9%)	27 (13%)	18 (13%)	17 (12%)	34 (17%)	25 (18%)
Moderately better	13 (9%)	17 (8%)	19 (13%)	23 (16%)	27 (13%)	19 (13%)	34 (24%)	42 (21%)	30 (21%)	48 (34%)	50 (25%)	26 (18%)	50 (35%)	54 (27%)	24 (17%)
Minimally better	36 (25%)	53 (26%)	27 (19%)	40 (28%)	69 (34%)	48 (34%)	41 (29%)	64 (32%)	49 (35%)	37 (26%)	63 (31%)	49 (35%)	37 (26%)	64 (32%)	41 (29%)
No change	83 (58%)	116 (57%)	86 (61%)	67 (47%)	85 (42%)	63 (44%)	51 (36%)	71 (35%)	47 (33%)	41 (29%)	59 (29%)	44 (31%)	33 (23%)	45 (22%)	46 (32%)
Minimally worse	4 (3%)	0	1 (1%)	4 (3%(	3 (1%)	1 (1%)	3 (2%)	1 (0%)	3 (2%)	1 (1%	2 (1%)	5 (4%)	5 (3%)	5 (2%)	6 (4%)
Moderately worse	0	0	0	0	0	0	1 (1%)	2 (1%)	0	0	1 (<1%)	0	0	1 (0%)	0
Markedly worse	0	1 (<1%)	0	0	1 (<1%)	0	0	0	0	0	0	0	1 (1%)	0	0
p-value versus NTG		0.4	0.5		0.7	0.5		0.9	0.8		0.8	0.2		0.6	0.2
p-Value versus NAT			0.8			0.96			0.96			0.2			0.03*

Table 23 lists at the p-values for symptom change among those who were catheterized and those not catheterized. The only group that differed were those catheterized. (Comment: This reviewer is concerned that knowledge of wedge pressure effects could have somehow amplified any benefit in symptoms only among catheterized subjects.).

Table 23. P-values for symptom assessment

	0.25 Hours			0.5 Hours			1 Hour			2 Hour			3 Hour		
	NTG N=143	NAT N=204	PBO N=142	NTG N=143	NAT N=204	PBO N=142	NTG N=143	NAT N=204	PBO N=142	NTG N=143	NAT N=204	PBO N=142	NTG N=143	NAT N=214	PBO N=142
Catheterized															
p-value versus NTG		0.6	0.7		0.7	0.9		0.3	0.96		0.8	0.4		0.4	0.3
p-Value versus NAT			0.9			0.5			0.3			0.2			0.03*
Not Catheterized															
p-value versus NTG		0.5	0.6		0.8	0.3		0.5	0.8		0.4	0.3		0.96	0.4
p-Value versus NAT			0.8			0.5			0.3			0.8			0.4

Table 24 Patient's Global Clinical evaluation

	0.25 Hours			0.5 Hours			1 Hour			2 Hour			3 Hour		
	NTG N=143	NAT N=204	PBO N=142	NTG N=143	NAT N=204	PBO N=142	NTG N=143	NAT N=204	PBO N=142	NTG N=143	NAT N=204	PBO N=142	NTG N=143	NAT N=214	PBO N=142
Markedly better	7 (5%)	11 (5%)	8 (6%)	8 (6%)	14 (7%)	9 (6%)	8 (6 %)	17 (8%)	13 (9%)	14 (10%)	21 (10%)	18 (13%)	16 (11%)	28 (14%)	21 (15%)
Moderately better	11 (8%)	17 (8%)	14 (10%)	18 (13%)	25 (12%)	18 (13%)	31 (22%)	43 (21%)	24 (17%)	38 (27%)	52 (26%)	26 (18%)	48 (34%)	55 (27%)	26 (18%)
Minimally better	37 (26%)	58 (29%)	32 (23%)	46 (32%)	69 (34%)	44 (31%)	45 (31%)	65 (32%)	51 (36%)	41 (29%)	59 (29%)	49 (35%)	30 (21%)	69 (34%)	45 (32%)
No change	85 (60%)	113 (56%)	88 (62%)	64 (45%)	91 (45%)	68 (48%)	53 (37%)	73 (36%)	50 (35%)	41 (29%)	66 (33%)	44 (31%)	41 (29%)	44 (22%)	45 (32%)
Minimally worse	2 (1%)	3 (1%)	0	4 (3%)	4 (2%)	3 (2%)	5 (3%)	5 (2%)	3 (2%)	6 (4%)	4 (2%)	5 (4%)	6 (4%)	7 (3%)	5 (4%)
Moderately worse	0	0	0	0	0	0	1 (1%)	0	0	0	0	0	2 (1%)	0	0
Markedly worse	0	1 (<1%)	0	0	0	0	0	0	0	0	0	0	0	0	0
p-value versus NTG		0.5	0.8		0.6	0.8		0.4	0.6		0.98	0.3		0.3	0.5
p-Value versus NAT			0.7			0.7			0.8			0.3			0.07

Table 25 lists the global symptom change among those who were catheterized and those not catheterized. The results for global symptoms are fairly similar to that of dyspnea. The data is graphically displayed as Figure 7

Table 25: P-values for global symptom assessment

	0.25 Hours			0.5 Hours			1 Hour			2 Hour			3 Hour		
	NTG N=143	NAT N=204	PBO N=142	NTG N=143	NAT N=204	PBO N=142	NTG N=143	NAT N=204	PBO N=142	NTG N=143	NAT N=204	PBO N=142	NTG N=143	NAT N=214	PBO N=142
Catheterized															
p-value versus NTG		0.7	0.98		0.6	0.9		0.5	0.8		0.9	0.9		0.3	0.8
p-Value versus NAT			0.7			0.5			0.8			0.7			0.1
Not Catheterized															
p-value versus NTG		0.6	0.8		0.8	0.6		0.6	0.7		0.8	0.2		0.7	0.6
p-Value versus NAT			0.8			0.8			0.94			0.3			0.3

Figure 6

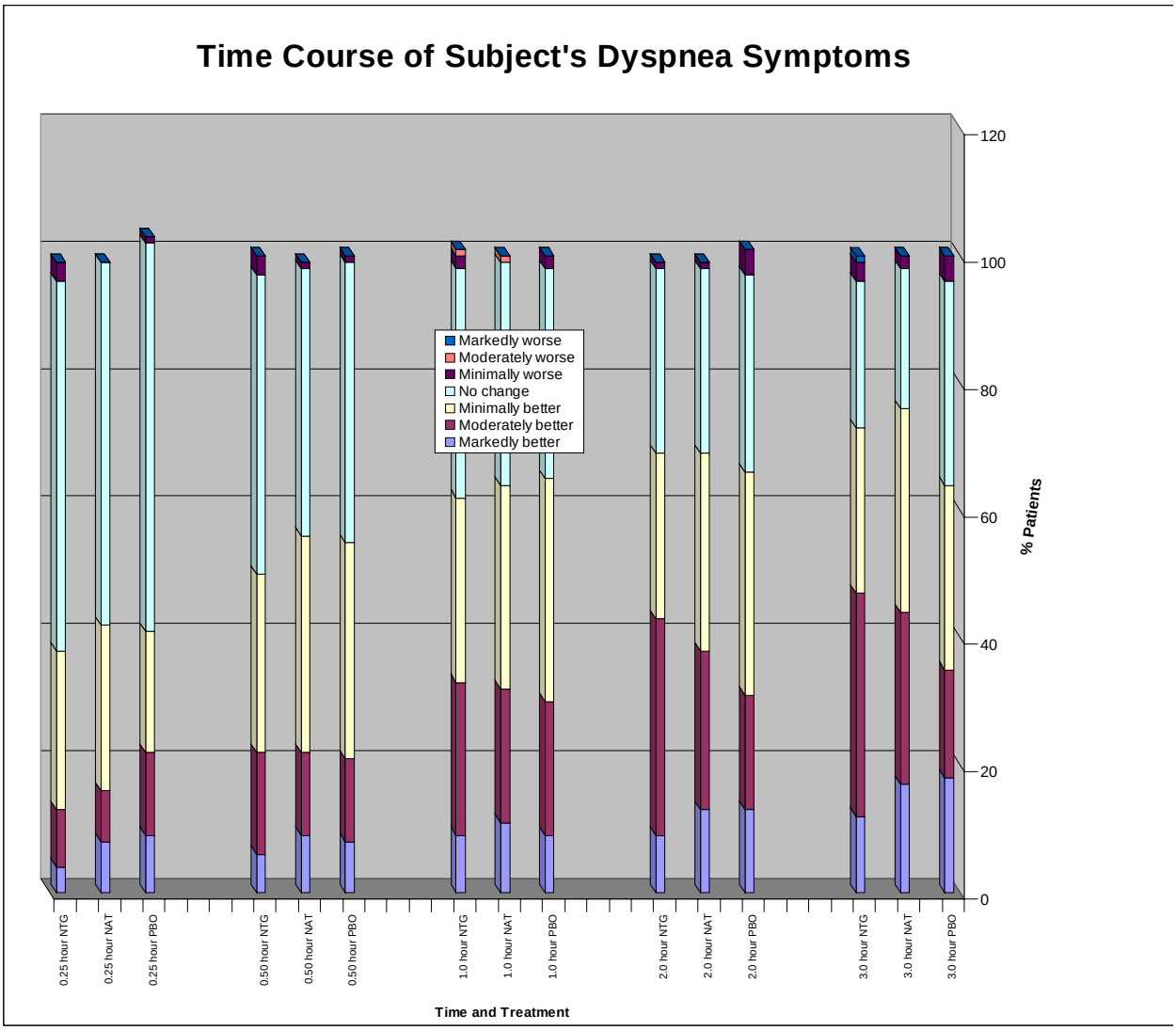
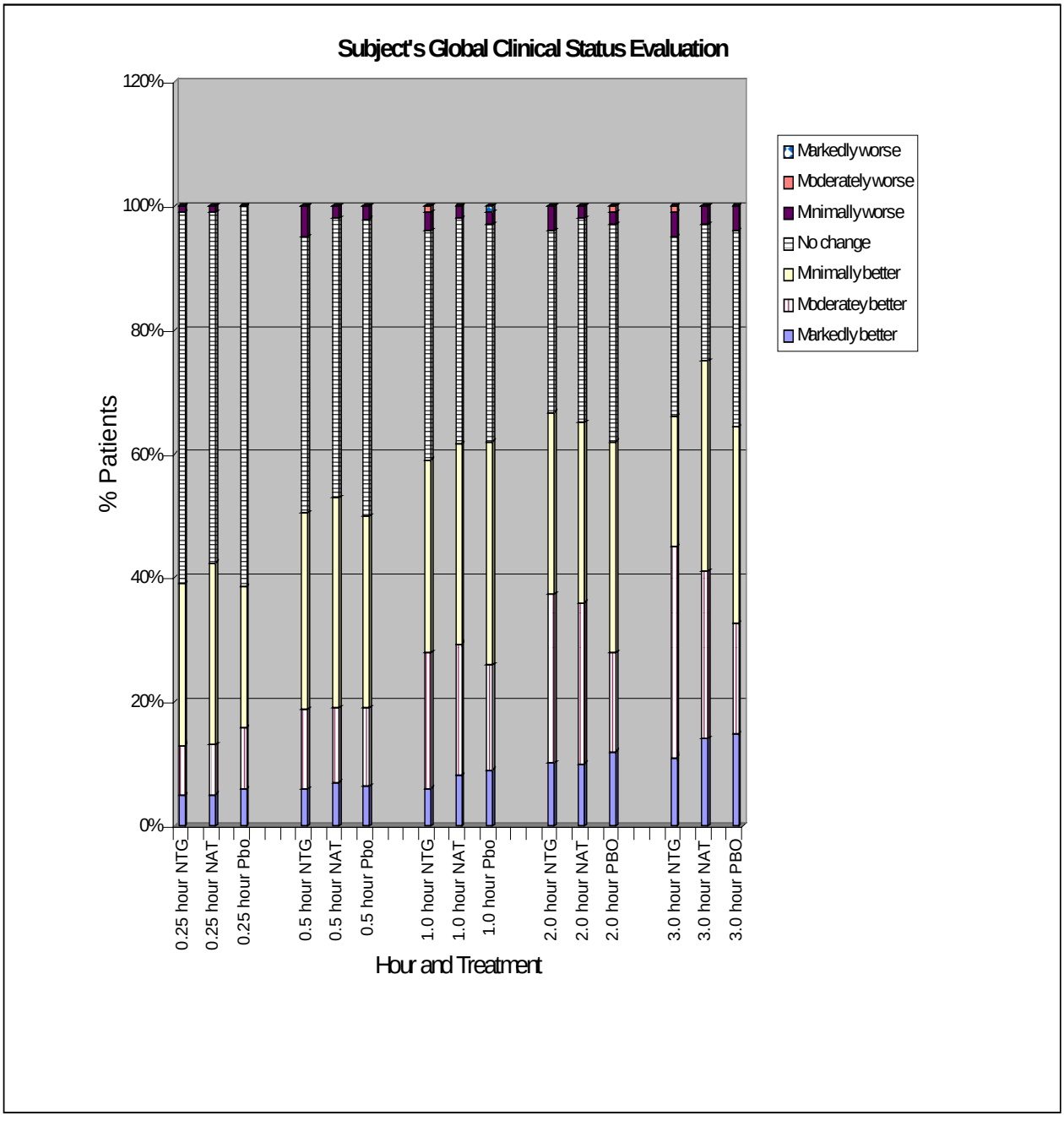

Time Course of Subject's Dyspnea Symptoms
Markedly worse
Moderately worse
Minimally worse
No change
Minimally better
Moderately better
Markedly better
120
100
80
60
40
20
0
% Patients
0.25 hour NTG
0.25 hour NAT
0.25 hour PBO
0.50 hour NTG
0.50 hour NAT
0.50 hour PBO
1.0 hour NTG
1.0 hour NAT
1.0 hour PBO
2.0 hour NTG
2.0 hour NAT
2.0 hour PBO
3.0 hour NTG
3.0 hour NAT
3.0 hour PBO
Time and Treatment

Figure 7.



With respect to global symptoms, there were no treatment differences during the initial three-hour evaluation when comparing nitroglycerin, Natrecor and placebo. Subject's global evaluation improved over time for all treatments. Few subjects had any deterioration during the initial three hours.

The effect during 24-hours:

Medications: The medications that were concomitantly used during the controlled period are shown in Table 26.

Table 26. Selected medications taken during 24-hour controlled period (PBO subjects have crossed over)

	Catheterized			Not Catheterized	
	NTG (n=92)	Natrecor Fixed (n=92)	Natrecor Adjustable (n=62)	NTG (n=124)	Natrecor Fixed (n=119)
Diuretics	82 (89%)	77 (84 %)	49 (79 %)	116 (94%)	106 (89 %)
IV diuretics	70 (76%)	64 (70 %)	41 (66 %)	93 (75 %)	81 (68 %)
Oral diuretics	43 (47%)	44 (48 %)	20 (32%)	60 (48 %)	53 (45 %)
Digoxin	49 (53%)	60 (65 %)	30 (48 %)	76 (61 %)	68 (57%)
IV Digoxin	3 (3%)	2 (2%)	2 (3%)	4 (3%)	3 (3%)
ACE inhibitors	51 (55%)	52 (57 %)	32 (52 %)	71 (57 %)	67 (56 %)
Non-IV Nitrates	34 (37 %)	30 (33 %)	18 (29 %)	41 (33 %)	37 (31 %)
IV Nitroglycerine	1(1%)	0	0	0	0
Beta Blockers	25 (27 %)	24 (26 %)	21 (34%)	37 (30 %)	35 (29 %)
IV Beta blockers	1(1%)	0	0	0	3 (3%)
Angiotensin II Blockers	8 (9 %)	5 (5%)	4 (6%)	11 (9%)	9 (8 %)
Dobutamine	24 (26%)	24 (26%)	21(34%)	9 (7 %)	26 (22 %)
Continued at Baseline	14 (15%)	13 (14%)	13 (21%)	7 (6%)	22 (18%)
New Administration	10 (11%)	11 (12%)	8 (13%)	2 (2%)	4 (3%)
PDE inhibitors	0	0	0	0	0
Dopamine	5 (5 %)	4 (4%)	8 (13 %)	2 (2%)	11 (9%)
Continued at Baseline	3 (3%)	3 (3%)	8 (13%)	0	8 (7%)
New Administration	2 (2%)	1 (1%)	0	2 (2%)	3 (3%)
Nitroprusside	0	1 (1 %)	0	0	0
Pressors	0	0	0	0	0

There were several differences in the nature of concomitant medications used during this portion of the study, this reviewer, however, could not interpret these changes as indicating a relative benefit in any particular treatment. There were more subjects in NTG than Natrecor group who received intravenous diuretics during the 24-hours of the study. Dobutamine was administered to approximately 25% of those who entered this portion of the study. The number of subjects who had new addition of dobutamine was greater among those catheterized than not-catheterized (12% versus 3%), but there did not appear to be a concentration of these subjects in any one treatment group. More Natrecor subjects were treated with dopamine during the 24-hour period; few of these subjects were newly treated. This reviewer cannot ascertain whether there was a difference in the number of subjects that were discontinued from pressors or after load reducers as a consequence of the added intravenous infusion.

Hemodynamics post-3 hours:

After 3 hours, several changes to the infusion occurred. Those who were randomized to placebo were crossed over to either fixed dose Natrecor or NTG. In addition, those subjects in the adjustable dose group could have their doses increased. The intent was to pool those on treatment (even placebo crossover subjects) despite the differences in the duration of exposure to infusion.

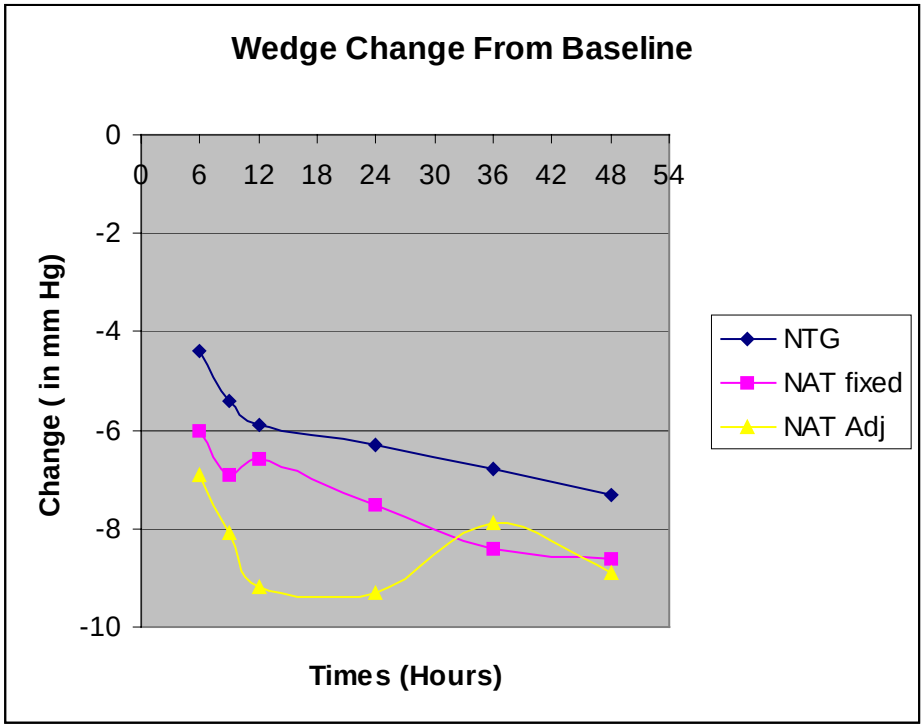
PCWP: The effect on wedge pressure is shown in Table 27. The placebo group was crossed over to the individual treatments. The baseline value for those who crossed over was the last measurement (the 3-hour measurement). The effect for the first 24-hours is credible. Results after 24-hours is distorted by the large number of subjects who discontinued at 24-hours, having completed the pre-

specified time of infusion. There did not appear to be a waning of effect of fixed Natrecor when compared to nitroglycerin during the observation period. Compared to NTG, Natrecor fixed dose was not superior at any time point. Compared to NTG, Natrecor, adjustable dose was superior to NTG at 6, 9, 12 and 24 hours. Values after 24 hours are less reliable due to the large number of subjects no longer treated.

Table 27. PCWP measurements post 3-hours.

		NTG N=92	Natrecor Fixed Dose N=92	Natrecor Adjustable dose N=62
Baseline	N = /Missing ( )	92 (0)	92 (0)	62 (0)
	Mean + SD	27.2 + 6.8	27.4 + 5.8	27.4 + 7.7
6 Hr	N= / missing in ( )	85 (7)	85 (7)	61 (1)
	Change from Baseline (LS mean + SE)	-4.4 + 0.7	-6.0 + 0.7	-6.9 + 0.9
	p-value versus NTG		0.1	0.03
	p-value versus NAT-Fixed			0.4
9 Hr	N= / missing in ( )	85 (7)	86 (6)	62 (0)
	Change from Baseline (LS mean + SE)	-5.4 + 0.8	-6.9 + 0.7	-8.1 + 0.9
	p-value versus NTG		0.15	0.02
	p-value versus NAT-Fixed			0.297
12 Hr	N= / missing in ( )	83 (9)	84 (8)	61 (1)
	Change from Baseline (LS mean + SE)	-5.9 0.7	-6.6 0.5	-9.2 + 0.9
	p-value versus NTG		0.2	0.001
	p-value versus NAT-Fixed			0.02
24 Hrs	N= / missing in ( )	84 (8)	86 (6)	57 (5)
	Change from Baseline (LS mean + SE)	-6.3 + 0.8	-7.5 + 0.8	-9.3 +1.0
	p-value versus NTG		0.3	0.016
	p-value versus NAT-Fixed			0.1
36 Hrs	N= / missing in ( )	47 (45)	36 (56)	34 (28)
	Change from Baseline (LS mean + SE)	-6.8 + 1.2	-8.4 + 1.3	-7.9 + 1.4
	p-value versus NTG		0.3	0.5
	p-value versus NAT-Fixed			0.8
48 Hrs	N= / missing in ( )	29 (63)	25 (67)	22 (40)
	Change from Baseline (LS mean + SE)	-7.3 + 1.4	-8.6 + 1.5	-8.9 + 1.6
	p-value versus NTG		0.5	0.4
	p-value versus NAT-Fixed			0.9

Figure 8



Other Hemodynamic measurements: Other hemodynamic parameters were measured at baseline and 24 hours. The results are shown in Table 28. Compared to NTG, only the RAP at 24-hours for the adjustable dose Natrecor differed from nitroglycerin.

Table 28. Hemodynamic positive-controlled, double blind period.

		NTG N=92	Natrecor Fixed Dose N=92	Natrecor Adjustable dose N=62
Mean Right Atrial Pressure				
Baseline	N = /Missing ( )	90 (2)	90 (2)	57 (5)
	Mean + SD	15.3 + 6.9	14.8 + 6.9	14.5 + 6.1
24 hours	N= / missing in ( )	87 (5)	89 (3)	58 (4)
	Change from Baseline (LS mean + SE)	-3.4 + 0.6	-4.3 + 0.6	-5.2 + 0.7
	p-value versus NTG		0.2	0.05
	p-value versus NAT-Fixed			0.3
Systemic vascular Resistance				
Baseline	N = /Missing ( )	87 (5)	89 (3)	56 (6)
	Mean + SD	1439 +641	1441+ 554	1411 + 572
24 hours	N= / missing in ( )	83 (9)	86 (6)	56 (6)
	Change from Baseline (LS mean + SE)	-209 + 60	-222 + 058	-175 + 74
	p-value versus NTG		0.9	0.7
	p-value versus NAT-Fixed			0.6
Cardiac Index L/min/m2				
Baseline	N = /Missing ( )	88 (4)	91 (1)	57 (5)
	Mean + SD	2.2 + 0.8	2.1 + 0.7	2.3 + 0.8
24 hours	N= / missing in ( )	84 (8)	89 (3)	58 (4)
	Change from Baseline (LS mean + SE)	0.2 + 0.08	0.2 + 0.07	0.1 + 0.09
	p-value versus NTG		0.95	0.15
	p-value versus NAT-Fixed			0.1
Pulmonary Vascular Resistance				
Baseline	N = /Missing ( )	83 (9)	80 (12)	51 (11)
	Mean + SD	259 + 174	266 + 174	233 + 162
24 hours	N= / missing in ( )	74 (18)	81 (11)	49 (13)
	Change from Baseline (LS mean + SE)	-40 + 18	-42 + 17	-40 + 22
	p-value versus NTG		0.9	0.1
	p-value versus NAT-Fixed			0.1
Mean Pulmonary Artery Pressure				
Baseline	N = /Missing ( )	92 (0)	91 (1)	61 (1)
	Mean + SD	38.5 + 8.8	38.3 + 7.7	38.1 + 8.8
24 hours	N= / missing in ( )	87 (5)	91 (1)	60 (2)
	Change from Baseline (LS mean + SE)	-5.6 + 0.9	-7.5 + 0.9	-7.8 + 1.1
	p-value versus NTG		0.1	0.1
	p-value versus NAT-Fixed			0.8

Dyspnea post-3 hours: Changes in Dyspnea symptoms were measured at 6 and 24 hours. The results are shown in Table 29. There was a clear time-dependent effect, with subjects improving in their dyspnea symptoms over time. There was no obvious benefit when Natrecor is compared to nitroglycerin at either at 6 or 24 hours, in considering the total population or those catheterized. There was, however, an effect, among those not catheterized that suggested a benefit in this subgroup (this is a subgroup of a secondary endpoint). There are no corresponding hemodynamics measurements for those not catheterized.

Table 29 Dyspnea Index post 3-hours.

	All Subjects		Catheterized		
	NTG total	Natrecor Total	NTG Catheterized	NAT Cath Fixed	NAT cath Adjust
6-Hours					
Number enrolled	N=216	N=273	N=92	N=92	N=62
Number with data	N=214	N=265	N=92	N=90	N=57
Markedly better	38 (18%)	57 (22%)	14 (15%)	14 (16%)	15 (26%)
Moderately better	67 (31%)	77 (29%)	28 (30%)	32 (36%)	11 (19%)
Mildly better	54 (25%)	71 (27%)	28 (30%)	22 (24%)	22 (39%)
No change	52 (24%)	56 (21%)	20 (22%)	19 (21%)	9 (16%)
Mildly worse	3 (1%)	2 (1%)	2 (2%)	1 (1%)	0
Moderately worse	0	1 (< 1%)	0	1 (1%)	0
Markedly worse	0	1 (< 1%)	0	1 (1%)	0
p-value NTG All vs. NAT All	--------	0.4**	-------	--------	---------
p-value Vs NTG Cath	--------	---------	-------	0.7*	0.3*
p-value Vs. NAT Fixed Cath	---------	----------	-------	---------	0.5*
p-value Vs. NAT Cath	----------	----------	0.5*	---------	--------
24-Hours					
Number enrolled	N=216	N=273	N=92	N=92	N=62
Number with data	N=215	N=266	N=92	N=89	N=59
Markedly better	67 (31%)	100 (38%)	33 (36%)	29 (33%)	22 (37%)
Moderately better	76 (35%)	84 (32%)	28 (30%)	29 (33%)	18 (31%)
Mildly better	39 (18%)	53 (20%)	18 (20%)	17 (19%)	13 (22%)
No change	29 (13%)	28 (11%)	11 (12%)	14 (16%)	5 (8%)
Mildly worse	2 (1%)	0	2 (2%)	0	0
Moderately worse	2 (1%)	1 (<1%)	0	0	1 (2%)
Markedly worse	0	0	0	0	0
P-value NTG All Vs. NAT All	--------	0.1**	-------	-------	-------
p-value Vs. NTG Cath	--------	---------	-------	0.7*	0.8*
p-value Vs. NAT Fixed Cath	---------	----------	-------	-------	0.5*
p-value Vs. NAT Cath	----------	----------	0.93*		

	Not catheterized	
	NTG total	Natrecor Total
6-Hours		
Number enrolled	N=124	N=119
Number with data	N=122	N=118
Markedly better	24 (20%)	28 (24%)
Moderately better	39 (32%)	34 (29%)
Mildly better	26 (21%)	27 (23%)
No change	32 (26%)	28 (24%)
Mildly worse	1 (1%)	1(1%)
Moderately worse	0	0
Markedly worse	0	0
p-value NTG Vs. NAT not cath	--------	0.8*
24-Hours		
Number enrolled	N=124	N=119
Number with data	N=123	N=118
Markedly better	34 (28%)	49 (42%)
Moderately better	48 (39%)	37 (31%)
Mildly better	21 (15%)	23 (19%)
No change	18 (15%)	9 (8%)
Mildly worse	0	0
Moderately worse	2 (2%)	0
Markedly worse	0	0
P-value NTG Vs. NAT not cath	--------	0.03*

* Wilcoxon ** ANOVA (treatment and catheter placement as covariates)

Global post 3 hours

Global symptoms of heart failure are shown in Table 30. Assessments were performed both at 6 and 24 hours. Here too, there was a time dependent improvement in symptoms over time. There were no significant differences in comparing those treated with nitroglycerin to those treated with Natrecor, when considering the population as a whole or limiting the analysis to those catheterized. There was, however, an effect, among those not catheterized which suggested a benefit in this subgroup (this is a subgroup of a secondary endpoint).

Table 30 Global Symptoms (p-value are nominal)

	All subjects		Catheterized subjects		
	NTG total	Natrecor Total	NTG Catheterized	NAT Cath Fixed	NAT cath Adjust
6-Hours					
Number enrolled	N=216	N=273	N=92	N=92	N=62
Number with data	N=215	N=264	N=92	N=89	N=57
Markedly better	35 (16%)	54 (20%)	15 (16%)	13 (15%)	13 (23%)
Moderately better	61 (28%)	84 (32%)	26 (28%)	31 (35%)	16 (28%)
Mildly better	63 (29%)	65 (25%)	30 (33%)	22 (25%)	19 (33%)
No change	51 (24%)	56 (21%)	19 (21%)	20 (22%)	9 (16%)
Mildly worse	4 (2%)	5 (2%)	2 (2%)	3 (3%)	0
Moderately worse	1 (0%)	0	0	0	0
Markedly worse	0	0	0	0	0
p-value NTG total Vs. NAT Total	--------	0.4**	-------	--------	---------
p-value Vs. NTG	--------	---------	-------	0.97*	0.2*
p-value Vs. NAT Fixed	---------	----------	-------	---------	0.3*
p-value Vs. NAT	----------	----------	0.5*	---------	--------
24-Hours					
Number enrolled	N=216	N=273	N=92	N=92	N=62
Number with data	N=214	N=265	N=92	N=89	N=58
Markedly better	60 (28%)	89 (34%)	29 (32%)	24 (27%)	20 (34%)
Moderately better	77 (36%)	91 (34%)	31 (34%)	30 (34%)	19 (33%)
Mildly better	37 (17%)	55 (21%)	15 (16%)	22 (25%)	12 (21%)
No change	34 (16%)	27 (10%)	13 (14%)	12 (13%)	6 (10%)
Mildly worse	3 (1%)	1 (< 1%)	3 (3%)	0	0
Moderately worse	3 (1%)	2 (1%)	1 (1%)	1 (2%)	0
Markedly worse	0	0	0	0	0
P-value NTG total Vs. NAT Total	--------	0.075**	-------	-------	-------
p-value Vs. NTG	--------	---------	-------	0.7*	0.6*
p-value Vs. NAT Fixed	---------	----------	-------	-------	0.3*
p-value Vs. NAT	----------	----------	0.5*		

	Not catheterized	
	NTG total	Natrecor Total
6-Hours		
Number enrolled	N=124	N=119
Number with data	N=123	N=118
Markedly better	20 (16%)	28 (24%)
Moderately better	35 (28%)	37 (31%)
Mildly better	33 (27%)	24 (20%)
No change	32 (26%)	27 (23%)
Mildly worse	2 (2%)	2(2%)
Moderately worse	1 (1%)	0
Markedly worse	0	0
p-value NTG Vs. NAT not cath	--------	0.1*
24-Hours		
Number enrolled	N=124	N=119
Number with data	N=123	N=118
Markedly better	31 (25%)	45 (38%)
Moderately better	46 (38%)	42 (36%)
Mildly better	22 (18%)	21 (18%)
No change	21 (17%)	9 (8%)
Mildly worse	0	1 (1%)
Moderately worse	2 (2%)	0
Markedly worse	0	0
P-value NTG Vs. NAT not cath	--------	0.01*

* Wilcoxon ** ANOVA (treatment and catheter placement as covariates)

Respiratory Rates till 3 hours

Respiratory rates were collected at baseline and 1 and 3 hours during the infusion are shown in Table 31. There were modest decreases in the respiratory rate for all treatments. None of the differences was significant (nominal p-values).

Table 31 Respiratory rates till 3 hours

	All subjects			
	NTG (N=143)	NAT (N=204)	PBO (N=142)	
Baseline Mean ± SD	23.2 ± 4.8	22.4 + 4.8	22.4 + 4.7	
1 hour				
N= /missing ( )	143 /(0)	201 /(3)	142 /(0)	
LS mean ± SE	-1.1 ± 0.3	-0.9 + 0.3	-0.8 + 0.3	
p-Value Vs. NTG		0.6	0.6	
p-Value Vs. NAT			0.91	
3 hours				
N= /missing ( )	141 /(2)	198 /(6)	138 /(4)	
LS mean ± SE	-1.4 ± 0.4	-1.3 + 0.3	-0.6 + 0.4	
p-Value Vs. NTG		0.91	0.1	
p-Value Vs. NAT			0.1	

In considering only those subjects catheterized, there was no difference in respiratory rates

Among those who were not catheterized, both Natrecor and NTG were marginally but not statistically different when compared to placebo (data not tabulated). At three hours there was a decrease in respiratory rate for NTG and NAT of –1.7 and –1.8 breaths/minute. For placebo the decrease was –0.2 breaths/min. Comparison of active treatments to placebo show a marginally significant decrease in respiratory rate (nominal p- values $0.1<p<0.05$).

Net fluid changes: The intake and output for the first 24 hours of infusion are shown in Table 32. There was a net output of more than 1 liter in each treatment group. Neither fluid intake nor fluid output differed among nitroglycerin or Natrecor. Since the fluid changes were measured over the 24-hour period, there was no placebo group for comparison

Table 32 Urine output ml/24 hours.

	NTG (N=216)	NAT Fixed (N=211)	ALL NAT (N=273)	NAT ADJ (N=62)
N=/ missing ( )	216 / (0)	208 (3)	270 (3)	62 / (0)
Fluid Intake Mean ± SD	1674 ± 664	1710 ± 588	1709 ± 626	1705 ± 745
N=/ missing ( )	214 / (2)	209 / (2)	270 / (3)	61 (1)
Urine Output Mean ± SD	-2959 ± 1543	-3019 ± 1752	-2969 ± 1838	-2797 ± 2113
N=/ missing ( )	214 / (2)	208 / (3)	269 / (4)	61 / (1)
Net Mean ± SD	-1279 ± 1455	-1308 ± 1613	-1257 ± 1657	-1082 ± 1799

Weight changes: Net weight changes are shown in Table 33. There were no differences in net weight change over the 24-hour period. The weight loss was consistent with the negative fluid balance.

Table 33 Weight Change 24 hours.

	NTG (N=216)	NAT Fixed (N=211)	ALL NAT (N=273)	NAT ADJ (N=62)
N=/ missing ( )	216 / (0)	211 (0)	273 (0)	62 / (0)
Baseline Mean + SD	84.8 ± 24.1	81.3 ± 19.7	81.5 ± 20.0	82.3 ± 21.2
N=/ missing ( )	208 / (8)	210 / (1)	272 / (1)	62 (0)
Net change Mean + SD	-1.1 ± 2.3	-1.4 ± 3.0	-1.4 ± 3.0	-1.3 ± 3.2

Sodium Excretion: Sodium excretion data was not collected.

Use of Diuretics: Diuretic use during the 24-hour period is shown in Table 34. The catheterized Natrecor adjustable dose had somewhat lower use of diuretics than the other groups. The mean dose was less among those not catheterized

Table 34 Use of diuretics.

	Catheterized			Non-Catheterized	
	NTG (n=92)	Natrecor Fixed Dose (n=92)	Natrecor Adjustable dose (n=62)	NTG (n=124)	Natrecor (n=119)
Number taking diuretic	82 (89%)	77 (84%)	49 (79%)	116 (94%)	106 (89%)
Not IV	70 (76%)	64 (70%)	41 (66%)	93 (75%)	81 (68%)
IV	43 (47%)	44 (48%)	20 (32%)	60 (48%)	53 (45%)
Mean dose/subject furosemide	172 ± 137	176 ± 157	173 ±150.	133 ± 91	136 ±120

Post-treatment medication: The list of medications used post treatment is shown in Table 35. For most subjects these reflect the treatments after 24-hours of the index infusion. For others who were treated for a longer duration, the medication list reflects post-treatment. There were few outstanding differences. Intravenous diuretics were used in 47-60% of those enrolled. PDE inhibitors were more frequently used in catheterized than in not catheterized subjects. Use of pressors (dobutamine, dopamine) was slightly less frequently used in the Natrecor adjustable group than in the other catheterized groups.

Table 35 Medications taken post treatment

	Catheterized			Not Catheterized	
	NTG (n=92)	Natrecor Fixed (n=92)	Natrecor Adj. (n=62)	NTG (n=124)	Natrecor (n=119)
Diuretics	76(83%)	77 (84 %)	45 (73 %)	99 (80 %)	96 (81 %)
IV diuretics	48 (52%)	55 (60 %)	32 (52 %)	58 (47 %)	63 (53 %)
Oral diuretics	58 (63%)	44 (48 %)	26 (42 %)	66 (53 %)	50 (42 %)
Digoxin	50 (54%)	51 (55 %)	30 (48 %)	69 (56 %)	53 (45 %)
IV Digoxin	1 (1%)	3 (3%)	2 (3%)	4 (3%)	4 (3%)
Aspirin	36 (39%)	36 (39 %)	28 (45 %)	52 (42 %)	52 (44 %)
ACE inhibitors	50 (54%)	53 (58 %)	35 (56 %)	70 (56 %)	58 (49 %)
Non-IV Nitrates	37 (40 %)	29 (32 %)	17 (27 %)	46 (37 %)	40 (34 %)
IV Nitroglycerine	6 (7%)	4 (4 %)	1 (2 %)	1 (1 %)	0
Beta Blockers	27 (29 %)	19 (21 %)	18 (29 %)	34 (27 %)	33 (28 %)
IV Beta blockers	1 (1%)	1 (1 %)	0	0	1(1%)
Anticoagulants:					
Warfarin	10 (11 %)	11 (12 %)	7 (11 %)	22 (18 %)	23 (19 %)
Heparin	13 (14%)	14 (15%)	9 (15%)	15 (12 %)	20 (17 %)
Statins	22 (24 %)	27 (29 %)	13 (21%)	25 (20 %)	21 (18 %)
Class III antiarrhythmics	9 (10 %)	23 (25 %)	17 (27 %)	12(20 %)	16 (13 %)
Calcium Channel Blockers	6 (7 %)	7 (8%)	9 (15 %)	10 (8 %)	23 (19 %)
Angiotensin II Blockers	9 (10 %)	7 (8%)	5 (8 %)	11 (9 %)	9 (8 %)
Hydralazine	13 (14 %)	7 (8 %)	12 (19 %)	10 (8 %)	6 (5 %)
Other antihypertensives	2 (2%)	3 (3%)	4 (6%)	2 (2 %)	8 (7 %)
Other antiarrhythmics	2 (2%)	4 (4 %)	2 (3 %)	6 (5 %)	6 (5%)
IIb/IIIa inhibitors	3 (3 %)	3 (3 %)	2 (3 %)	5 (4 %)	3 (3 %)
Dobutamine	33 (36 %)	31 (34%)	20 (32 %)	19 (15 %)	28 (24 %)
New Administration	20 (22%)	18 (20%)	10 (16%)	13 (10%)	7 (6%)
PDE inhibitors	12 (13%)	8 (9 %)	10 (16 %)	4 (3 %)	6 (5%)
Dopamine	10 (11 %)	9 (10 %)	9 (15%)	4 (3%)	14 (12%)
New Administration	7 (8%)	8 (9%)	2 (3%)	4 (3%)	7 (6%)
nitroprusside	4 (4%)	2 (2 %)	2 (3 %)	2 (2 %)	0
Pressors	0	2 (2%)	1 (2%)	0	0

Hospitalizations: Hospitalization Days were prolonged by approximately 2 days among the Natrecor-treated subjects when compared to the NTG group. There was a greater fraction of those treated with Natrecor who were still hospitalized at 30 days post-enrollment. Among those discharged, slightly more Nitroglycerin subjects were readmitted during the 30-day post-infusion

period. The fewest number of readmissions were among those in the Natrecor adjustable dose group. The differences, however, were small. The most common causes of rehospitalization were acute events.

Table 36 Current hospitalization and hospitalization till 30 days.

	NTG (N= 216)	NAT Fixed (N=211)	All NAT (N=273)	NAT ADJ (N= 62)
Days Hops prior to Infusion Mean ± SD	1.9 ± 3.1	1.9 ± 2.7	1.8 ± 2.8	1.7 ± 3.0
N= / Missing ( )	216 /(0)	211 / (0)	273 /(0)	62 /(0)
Days Hosp. From Start of Infusion Through Day 30 Mean ± SD	8.1 ± 7.0	10.3 ± 8.7	10.0 ± 8.4	8.8 ± 7.2
N= / Missing ( )	216 (0)	211 (0)	273 / (0)	62 (0)
# Discharged prior to 30 days				
yes	206 (95%)	194 (92%)	253 (93%)	59 (95%)
no	10 (5%)	17 (8%)	20 (7%)	3 (5%)
Of Those Discharged, Those readmitted by day 30	48 (23%)	41 (21%)	50 (20%)	9 (15%)
1 readmission	39 (19%)	38 (20%)	47 (19%)	9 (15%)
2 readmissions	9 (4%)	3 (2%)	3 (1%)	0
3 readmissions	0	0	0	0
4 readmissions	0	0	0	0
Total readmissions	57	44	53	9
Reason for Readmission				
Acute CHF	30 (14%)	18 (9%)	21 (8%)	3 (5%)
CHF elective	0	0	0	0
Other, Acute	23(11%)	23 (11%)	27 (10%)	4 (6%)
Other elective	4 (2%)	3(1%)	5 (2%)	2 (3%)

Mortality: Mortality was to be assessed at 30, 90 and 180 days after the infusion. A Kaplan-Meier representation of the mortality is shown as figure 9. Point estimates actually favor Nitroglycerine (Table 37). There was no benefit of the use of Natrecor on mortality. At one month, the worst outcome was in the Natrecor Adjustable dose (11.5% mortality rate). At six-months the mortality rate mortality rate for this cohort was 35%.

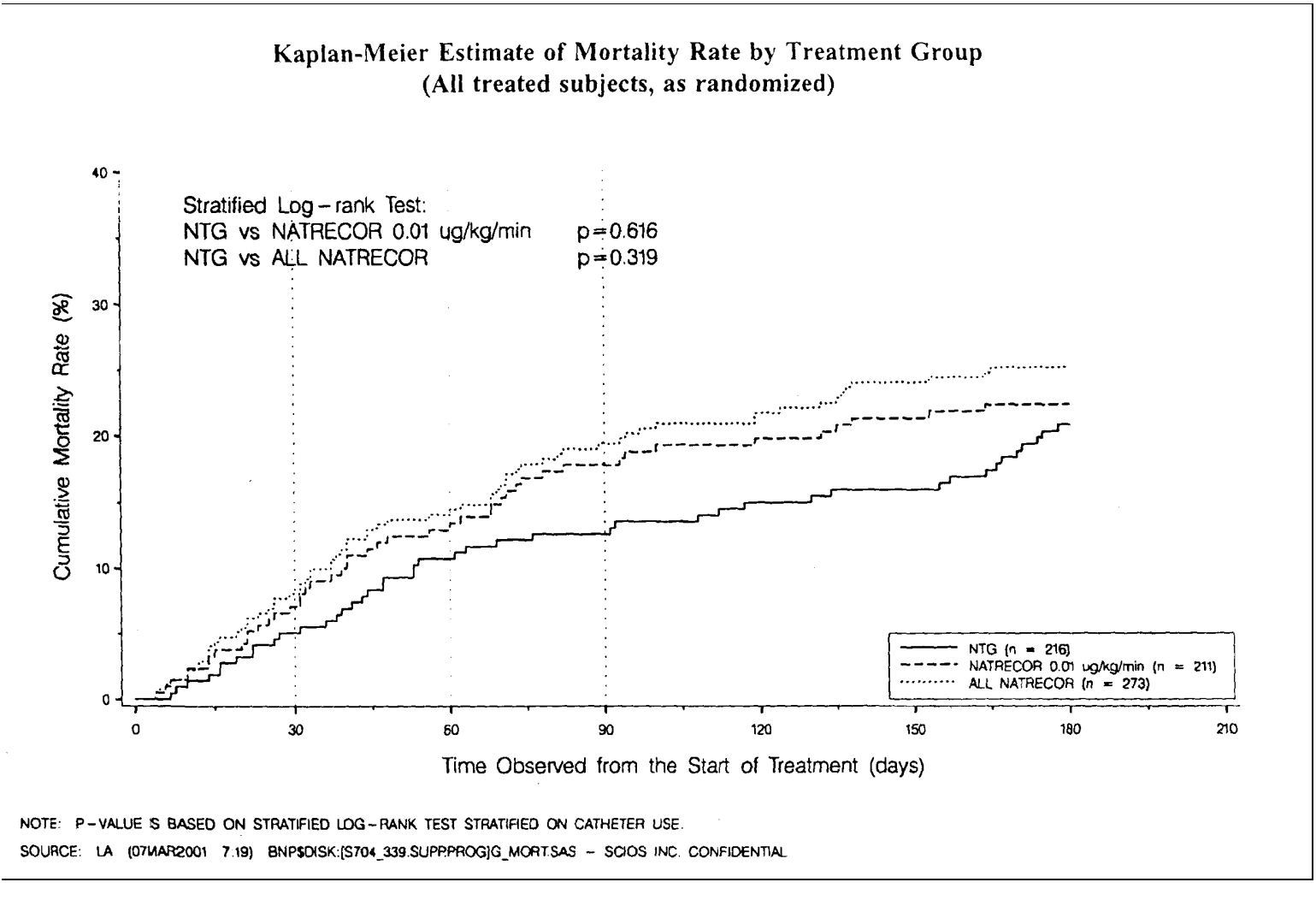
The risk ratio for death comparing the various Natrecor cohorts to the Nitroglycerin cohort ranged from 1.4 to 1.6 at 30-days. Confidence intervals were wide. At 90 days, the risk ratio comparing the cohorts off Natrecor to Nitroglycerin was between 1.4 to 1.5. At 6 months, the risk ratio again favored nitroglycerin and ranged from 1.1 to 1.2 for the Natrecor fixed and All Natrecor respectively. The risk ratio for the Natrecor adjustable dose at 6 months, compared to nitroglycerin catheterized patients was 1.6. None of these estimates of the relative hazard of death differed significantly from each other. Although the risk ratio favored nitroglycerin, the confidence intervals were large. It is unclear if the negative risk ratio is real or merely the play of chance. The sponsor attributes the differences in mortality to imbalance in the severity of disease at baseline.

Table Mortality at 30 days (1-month), 90 days (3-months) and 180 days (6-months)

	Summary			Catheterized			Not Catheterized	
	NTG	Natrecor Fixed	All Natrecor	NTG	Natrecor Fixed	Natrecor Adj	NTG	Natrecor Fixed
N=	216	211	273	92	92	62	124	119
# Deaths by 1 month	11 (5.1%)	15 (7.1%)	22 (8.1%)	7 (7.6%)	5 (5.4%)	7 (11.5%)	4 (3.2%)	10 (8.4%)
# Censored by 1 month[1]	1	2	3	0	0	1	1	2
p-value[2] compared to NTG	-----	0.4	0.2	-----	0.5	0.4	-----	0.08
Risk Ratio [3](NAT/NTG) CI	-----	1.4 0.6-3.1	1.6 0.8-3.2	-----	0.7 0.2-2.2	1.55 0.5-4.4	-----	2.7 0.8-8.6
# Deaths by 90-days	27 (13%)	37 (18%)	52 (19%)	Not analyzed				
# Censored by 90-days								
p-value[2] compared to NTG	------	0.15	0.08					
Risk Ratio [3](NAT/NTG) CI	-----	1.44 0.8-1.7	1.52 0.8-1.8					
# Deaths by 6 months	44 (21%)	46 (22%)	67 (25%)	22 (24%)	23 (25%)	21 (35%)	22 (18%)	23 (20%)7
# Censored by 6 months[4]	8	10	12	2	2	2	6	8
p-value[2] compared to NTG	------	0.6	0.3	----	0.8	0.1	----	0.6
Risk Ratio [3](NAT/NTG) CI	-----	1.11 0.7-1.7	1.22 0.8-1.8	-----	1.1 0.6-1.9	1.6 0.9-2.9	-----	1.2 0.6-2.1

[1] These were subjects lost to follow up by 30 days [2]p-value is based on stratified log rank test stratified on catheter use.
[3] Risk ratio was based on proportional hazard's model. [4] These were subjects lost to follow up by 180 days

Figure 9



Demographics and Efficacy on PCWP: Dr. Hung of the FDA analyzed these subgroups.

Table 38. Change in wedge pressure mean ± SE(?)

	Treatments		
	Nitroglycerin	Natrecor	Placebo
Gender			
Male	N=43; -3.6 ± 0.9	N=92 ; -5.9 ±0.7	N=47 ; -1.9 ± 0.6
Female	N=16; -4.5 ± 1.1	N=29 ; -5.5 ± 1.0	N=15; -2.3 ± 1.3
Race			
Caucasian	N=33; -2.6 ± 0.9	N=74; -5.4 ± 0.8	N=39; -2.2 ± 0.6
Blacks	N=17 ; -5.9 ± 1.1	N=30 –5.9 ± 0.9	N=14 ; -0.6 ± 1.2
Hispanic	N=9 ; -4.2 ±1.8	N=15; -7.0 ± 1.5	N=8; -3.4 ± 2.2
Other	N=1; -21		
Age			
< 65 years old	N=40 –4.5 ± 0.8	N=70; -6.2 ± 0.8	N=37; -1.5 ± 0.8
≥ 65 years old	N=19; -2.4 = 1.1	N=51; -5.3 ± 0.9	N=25; -2.9 ± 0.7
NYHA Class			
Class I	N=0	N=1; -5.0	-----
Class II	N=10; -4.1 ± 1.4	N=9; -5.2 ± 1.3	N=2; -7.5 ± 2.5
Class III	N=27; -4.7 ± 0.9	N=48; -7.2 ± 0.9	N=24; -2.0 ± 0.9
Class IV	N=18; -1.4 ± 1.3	N=54; -4.6 ± 1.0	N=31; -1.0 ± 0.6
No previous CHF	N=4; -8.0 ± 2.4	N=9 ; -6.8 ± 2.3	N=5; -6.8 ± 2.4

The subgroups were generally small and do not allow a definitive conclusion to be drawn.

Demographics on symptom benefit:

	Treatments		
	Nitroglycerin	Natrecor	Placebo
Gender			
Male	N=86; 1.1 ± 0.1	N=147 ; 1.3 ±0.1	N=103 ; 1.0 ± 0.1
Female	N=57; 1.4 ± 0.1	N=56 ; 1.4 ± 0.2	N=39; 1.4 ± 0.2
Race			
Caucasian	N=85; 1.1 ± 0.1	N=117; 1.1 ± 0.1	N=83; 1.0 ± 0.1
Blacks	N=35 ; 1.6 ± 0.2	N=50 1.7 ± 0.1	N=34 ; 1.2 ± 0.2
Hispanic	N=19 ; 1.4 ±0.3	N=29; 1.3 ± 0.2	N=21; 1.4 ± 0.3
Other	N=4; 1.3 ± 0.3	N=7; 1.9 ± 0.3	N=4; 0.5 ± 0.3
Age			
< 65 years old	N=88 1.2 ± 0.1	N=118; 1.4 ± 0.1	N=73; 1.2 ± 0.1
≥ 65 years old	N=55; 1.3 = 0.1	N=85; 1.2 ± 0.1	N=69; 1.1 ± 0.1
NYHA Class			
Class I	N=; 2.0	N=1; 2.0	N=1 ; 0.0
Class II	N=18; 0.8 ± 0.2	N=13; 1.3 ± 0.1	N=7; 0.9 ± 0.5
Class III	N=57; 1.2 ± 0.1	N=88; 1.3 ± 0.1	N=59; 1.3 ± 0.1
Class IV	N=55; 1.2 ± 0.2	N=85; 1.2 ± 0.2	N=64; 0.9 ± 0.2
No previous CHF	N=12; 1.8 ± 0.3	N=16 ; 1.8 ± 0.3	N=11; 1.5 ± 0.4

The subgroups are small and no definitive conclusions are warranted.

Safety:

Duration of Exposure: The duration of exposure is shown in Table 40 (sponsors table 4.10).

Table 40 Duration of infusion

	Catheterized			Not Catheterized	
	NTG	NAT Fixed	NAT ADJ	NTG	NAT
Mean ± SD (Hours)	35.9 ± 17.5	34.4 ± 18.8	33.0 ± 16.3	35.8 ± 20.4	71.0± 350.7
Median (25%-75%)	26.6 (24-48)	24.5 (24-43)	24.5 (24-43)	24.4 (24-46)	24.4 (24-46)
Number with time of infusion (includes interruptions)					
0 hr	0	0	0	0	0
>0-3 hr	0	0	0	0	2 (2%)
>3-12 hr	4 (4%)	3 (3%)	3 (3%)	3 (2%)	3 (3%)
>12-24	13 (14%)	17 (18%)	14 (23%)	32 (26%)	25 (21%)
>24-48	57 (62%)	53 (58%)	34 (55%)	66 (53%)	67 (56%)
>48-72	15 (16%)	15 (16%)	10 (16%)	15 (12%)	10 (8%)
>72	3 (3%)	4 (4%)	1 (2%)	8 (6%)	12 (10%)

One subject in the not catheterized, NAT group received study-drug infusions for 161 days. The mean for this group is correspondingly distorted.

The mean dose for the NAT subjects was 0.01 ug/kg/min whether the subjects were or were not catheterized or were treated as a fixed or adjustable dose regimen. There were two subjects who were treated with the fixed dose regimen whose dose was increased to > 0.01 ug/kg/min. One subject's dose was between 0.1125 and 0.175 and the other subject 0.03 ug/kg/min. Among those in the adjustable dose NAT regimen, 27 subjects received doses of 0.01125 ug/kg/min or greater; 9 subjects received infusions of > 0.0225 ug/kg/min.

For those randomized to NTG groups (catheterized and not-catheterized), 87/ 216 subjects received infusions of > 20 ug/min and 33/216 received doses of > 80 ug/min. The mean doses at the various times for those catheterized and those not catheterized are shown in Figure 2.

Deaths/Dropouts/Discontinuations

There were a total of 36 subjects who were randomized who died during the 30-day observation period of the study. There were a total of four subjects who were lost to follow up and whose status at 30 days cannot be ascertained. Of the deaths, 33 received treatment and 3 died prior to the start of the infusion. There were 22 subjects that died who were treated with Natrecor (15 on the fixed dose and 7 on the adjustable dose regimens) and 11 subjects treated with nitroglycerine. No subjects died during the placebo portion or the study. The deaths are described below.

Randomized but not treated:

1) Subject # 642-501 (Natrecor Fixed Dose, not catheterized). This was a 74 y/o male with NYHA class IV CHF who was admitted shortly after sustaining a MI. his course was complicated by CHF and mitral regurgitation. The subject had a successful revascularization of the right coronary artery and obtuse marginal branch. His study drug was delayed due to hypotension. The subject arrested 2-hours later and died.

2) Subject # 687-411 (Natrecor fixed dose, catheterized). This was a 75-y/o male with NYHA Class IV CHF and a history of multiple myocardial infarctions, CABG and AICD implantation and also a history of IDDM and renal

insufficiency. He was admitted to the ICU with chest pain. A Swan Ganz catheter was inserted and he was intubated and ventilated. His troponin levels were elevated suggesting an acute MI as the etiology of his cardiac instability. The subject improved and was then randomized but suffered a cardiac arrest and died prior to the start of the infusion.

3) Subject # 540-406 (NTG, catheterized). This was a 46-y/o male with NYHA Class II CHF and idiopathic cardiomyopathy, and symptomatic bradycardia for which a DDD pacemaker was in place. The subject was randomized, but the PCWP dropped to below 14 mm Hg and study drug was not administered. The subject had a seizure with respiratory arrest and died the next morning.

Treated Subjects:

1) Subject # 369-407 (PBO/NTG, catheterized). This was a 64-y/o woman with NYHA Class III CHF due to ischemic cardiomyopathy. Concurrent conditions included peripheral vascular disease, hypertension, diabetes CAD and right ventricular failure. She completed the initial 24-hour infusion and was discharged on day 5. She was readmitted on day 11 for decompensated CHF. She was discharged on intravenous home dobutamine via a Hickman catheter. On day 25 her status decompensated. The following day she had a cardiac arrest and died.

2) Subject # 538-405 (NTG, catheterized). This was a 87-year old female with NYHA Class II CHF due to ischemic cardiomyopathy and a history of CAD, MI, atrial fibrillation, frequent PVCs a, first degree AV-nodal block and increase in cardiac enzymes. She was treated for 26 hours with study drug that was discontinued because she was feeling unwell. She was cardiac catheterized on day 4 (why???) which showed left main coronary and left anterior descending coronary artery disease. Because she did not qualify as a candidate for either angioplasty or bypass surgery she was transferred to a nursing home for hospice care and died on study day 10.

3) Subject # 618-401 (PBO/NTG, catheterized). This was a 41-y/o female with NYHA class IV CHF due to dilated cardiomyopathy and a history of ventricular septal defect with repair, paroxysmal atrial fibrillation, CVA, chronic renal insufficiency and apical thrombosis. She was treated for 44 hours with study drug that was discontinued due to lack of efficacy. She was started on dopamine but continued to deteriorate. She had an episode of VT requiring cardioversion on day 22. She arrested and died 7 hours later.

4) Subject # 627-507 (NTG, not catheterized). This was a 68-y/o male with NYHA class IV CHF due to ischemic cardiomyopathy and a history of MI, CABG, polymorphic VT requiring AICD placement, hypertension, renal insufficiency and hypothyroidism. The subject was hospitalized for fever, ascites, abdominal distention and decompensated CHF. Treatment for this subject included antibiotics, bowel rest and inotropic support. He was entered into this study and treated for 48 hours with study drug. He was discontinued due to lack of improvement. On day 5 he underwent a hemicolectomy and ileostomy for a perforated bowel. He died on day 15 due to ischemic cardiomyopathy, sepsis and ruptured bowel.

5) Subject #627-509 (NTG, not catheterized). This was a 90-y/o woman with NYHA class III CHF due to ischemic cardiomyopathy and CAD. She also had GE reflux. She was treated for 72 hours with study drug and was discontinued due to clinical improvement. She was discharged on day 7. On day 14 she arrested at home and died.

6) Subject # 636-505 (NTG, not catheterized). This was a 61-y/o male with NYHA Class IV CHF due to ischemic cardiomyopathy. Medical history included CAD, CABG, mitral valve repair, pacemaker placement, atrial fibrillation and hypertension. He was treated for 48 hours with study drug that was discontinued due to inadequate clinical response. He apparently had chronic renal failure that worsened during hospitalization. He died on day 22 due to respiratory failure, hyperthyroidism and sepsis (*enteobacter aerogens*).

7) Subject # 663-402 (NTG, catheterized). This was a 62-y/o male with NYHA class III CHF due to cardiomyopathy. He also had a history of atrial flutter, MI, chronic renal insufficiency and chronic venous stasis ulcers. He was treated for 4 days with study drug and concurrent dobutamine. The study drug was discontinued because of clinical improvement. Dobutamine was continued. On day 5 his renal function and CHF worsened. He was treated with dopamine, Diuril and Lasix. He developed pre-renal azotemia on day 6 and Lasix was held. He arrested on day 7 and died.

8) Subject # 678-403 (NTG, catheterized). This was a 44-y/o male with NYHA class III CHF due to idiopathic dilated cardiomyopathy, mitral regurgitation, CAD, previous MI and also a history of hypertension. He was treated with study drug for 67 hours and the infusion stopped because of clinical improvement. The subject was discharged on day 4. He was readmitted on day 10 due to shortness of breath and paroxysmal nocturnal dyspnea and was intubated. EKG showed sinus tachycardia. He was treated with Lasix, dopamine and milrinone, He died on day 26 due to heart failure.

9) Subject #679-402 (PBO/NTG, catheterized). This was a 73-y/o female with NYHA class IV CHF due to idiopathic dilated cardiomyopathy, a history of MI, AV nodal block (pacemaker placed) and hypertension. The infusion was discontinued due to inadequate clinical response. She was discharged to home on day 5. The subject died at home on day 8. (It is unclear if this was a witnessed demise or an unwitnessed sudden death.) The death was attributed to CHF.

10) Subject # 687-406 (PBO/NTG, catheterized). This was a 73-y/o male with NYHA Class IV CHF due to dilated ischemic cardiomyopathy and a history of left ventricular aneurysm, VT, AICD, COPD and diabetes. The subject was treated for approximately 3 days with study drug that was stopped due to inadequate clinical response. Milrinone was started when study drug was stopped. He had an episode of symptomatic hypotension that lasted 30 minutes. He was discharged home on study day 8, but was to return to the clinical to receive IV milrinone. On study day 16, the subject developed shortness of breath and overall weakness. He presented to the emergency department with pulseless electrical activity and died.

11) Subject # 687-502, (NTG, not catheterized). This was an 86-y/o male with NYHA class IV CHF due to ischemic cardiomyopathy and a history of CAD, MI, severe mitral regurgitation, atrial fibrillation and syncope. He was treated for approximately 40 hours with study drug, with the infusion stopped because of clinical improvement. The subject was discharged in day 4. He died on day 19 at home of CHF.

Natrecor subjects:

1) Subject #357-502 (Natrecor fixed dose, not catheterized) This was a 67-y/o female with NYHA class IV CHF of unknown etiology and a history of pulmonary hypertension, liver disease and Bence-Jones proteinemia. Dopamine was administered prior to the start of study drug She was treated for only 11 minutes before the infusion was stopped because of a sudden decrease in blood pressure. Her BP dropped from 94/47 to 70/25. An echocardiogram showed an ejection fraction of 20% and evidence of a restrictive cardiomyopathy (secondary to amyloidosis). On day 6 the subject had a cardio-respiratory arrest. She was intubated and transferred to CCU. She died on day 10. Autopsy confirmed amyloid heart disease.

[Comment: This is a patient with diastolic dysfunction whose blood pressure immediately bottomed post Natrecor treatment.]

2) Subject # 369-503 (Natrecor fixed dose, not catheterized). This was a 78-y/o male with NYHA class III due to non-ischemic cardiomyopathy and a history of atrial fibrillation, diabetes, hypertension and alcohol abuse. He was being treated with ongoing dopamine and dobutamine throughout the study infusion. He was treated with study drug for two days and discontinued due to inadequate clinical response. He developed sepsis on day 5, a GI bleed on day 8 acute renal failure requiring dialysis. On day 16 his CHF. He developed worsening dyspnea requiring dobutamine. He experienced a cardiac arrest on day 22 and died on day 26 with the death attributed to fulminant sepsis.

3) Subject # 538-401: (Natrecor Fixed dose, catheterized). This was a 72-y/o male with NYHA Class II CHF due to valvular heart disease and a history of tricuspid valve repair, CABG, paroxysmal atrial fibrillation, pulmonary hypertension who presented with dyspnea and pleural effusions. Wedge pressure on admission was 24 mm Hg. On day 3 his status worsened with severe shortness of breath. Bilateral plural effusions were noted on ultrasound and a thoracocentesis resulted in the removal of 500 cc of fluid. Though transiently improved, his status subsequently worsened and he required mechanical ventilation. His renal function also worsened. He died on day 15.

4) Subject # 539-502 (PBO/NAT fixed dose, not catheterized). This was a 55-y/o female with NYHA class IV CHF due to aortic insufficiency, Takayasu's arteritis, hypertension and fibromyalagia, She finished 24 hours of infusion with the infusion stopped because of clinical improvement. On day 5 she sustained a cardiac arrest and was resuscitated and ventilated. She died the next day.

5) Subject # 551-404 (PBO/NAT, fixed dose, catheterized). This was a 41-y/o female with NYHA Class IV CHF and a past history of cardiac transplantation in 1989 due to *post-partum* cardiomyopathy. She had biventricular heart failure due to accelerated graft atherosclerosis. She also had azotemia, hypertension, tachycardia and syncope. She was treated for 24-hours with study drug that was discontinued due to inadequate response. She was then started on dopamine. She was discharged for hospice care on day 8 and arrested on day 28 and died on day 29.

6) Subject 554-508 (Natrecor, fixed dose, not catheterized). This was a 55 y/o male with NYHA class IV CHF with a history of MI, CVA, hyperlipidemia and atrial fibrillation with a rapid ventricular response who was treated with study drug for 24-hours. The infusion was stopped due to clinical improvement. He had one episode of atrial fibrillation with a rapid response that was treated with metoprolol. He died on day 14 due after a cardiac arrest.

7) Subject # 572-411 (Natrecor fixed dose, catheterized). This was a 61-y/o male with NYHA class III CHF due to ischemic cardiomyopathy and a history of CAD, CABG, MI, polymorphic VT, diabetes and atrial fibrillation. He was treated for 48 hours with study drug but discontinued due to the lack of improvement in CI. Dobutamine wad added on day 2. On day 4 he was found unconscious and in agonal rhythm. The cause of death was attributed to polymorphic VT and underlying cardiomyopathy and coronary artery graft occlusion.

8) Subject #627-505 (Natrecor, fixed dose, not catheterized). This was a 71-y/o male with NYHA Class IV CHF due to idiopathic dilated cardiomyopathy and a history of CABG, pacemaker insertion for heart block, VT, renal insufficiency, pneumonia and prostatic hypertrophy. He was treated approximately 5 days with study drug that was discontinued due to clinical improvement. On day 10 he developed worsening CHF with increased SOB and worsening renal function (creatinine increased from 2.8 to 3.6 mg/dL) and decreased blood pressure. He died on day 20.

9) Subject # 627-506 (Natrecor, fixed dose, not catheterized). This was 63-y/o male with NYHA Class III CHF due to severe ischemic cardiomyopathy and a history of hypertension, left internal carotid artery stenosis, right axillary stenosis and renal artery stenosis. He was admitted for pulmonary edema associated with a non-Q wave MI. He was treated for 46 hours and discontinued due to clinical improvement. On day 7, he developed diaphoresis, sinus bradycardia and severe. He sustained an asystolic cardiac arrest and died.

10) Subject # 642-402 (Natrecor, fixed dose, catheterized). This was a 77-y/o female with NYHA Class III CHF due to ischemic cardiomyopathy, AICD placement, UTI, diabetes and esophageal dysmotility. She was treated for 24 hours with study drug and discontinued due to clinical improvement. She was readmitted on day 19 due to nausea, vomiting and UTI. On day 23, she developed hypotension and confusion leading to cardiogenic shock and death.

11) Subject # 663-413 (PBO/NAT, catheterized). This was a 72-y/o male with NYHA Class IV CHF due to ischemic cardiomyopathy and a history of CAD, CABG, AF, NSVT, sinus node disease, diabetes and hypertension. He was treated for 43 hours, with the infusion discontinued due to clinical response. He was discharged home but died on day 25 due to end-stage cardiomyopathy.

12) Subject # 666-502 (PBO/NAT, not catheterized). This was a 77-y/o male with NYHA Class IV CHF due to ischemic cardiomyopathy and a history of CAD, sick sinus syndrome, AICD placement, AF, sustained VT, diabetes and renal insufficiency. He was treated for 4 days with study drug that was discontinued due to lack of clinical response. On day 9, he developed pulmonary and renal failure and died on day 10.

13) Subject # 671-504 (Natrecor fixed dose, not catheterized). This was an 88-y/o male with NYHA class III CHF due to ischemic dilated cardiomyopathy and a history of CAD, CABG, hypertension, chronic renal disease AF, hypercholesterolemia, PVD and benign prostatic hypertrophy. He was treated for 24 hours with study drug that was discontinued due to clinical improvement. He had a single episode of asymptomatic hypotension that required a one-hour cessation of therapy. He was discharged on day 3. On day 14 he was admitted for the treatment of worsening CHF. On day 17, he underwent an angioplasty of the vein graft to the LAD. His condition deteriorated. On day 19 his creatinine level was 3.1 mg/dl (baseline was 1.8 mg/dl). On day 21 the subject died of CHF and renal failure

14) Subject # 678-515 (PBO/NAT fixed dose, not catheterized). This was a 77-y/o woman with NYHA Class IV CHF due to ischemic dilated cardiomyopathy and a history of MI, AF, sustained VT, VF with AICD placement, diabetes and hypertension. The subject was treated for 4 days and the infusion was discontinued due to inadequate clinical response.

The subject's condition continued to deteriorate. On day 19 her creatinine and BUN were 2.8 and 119 mg/dL, respectively. She died on day 21of severe left ventricular systolic function as a consequence of CAD, COPD and possibly sepsis.

15) Subject # 679-504 (PBO/NAT fixed dose, not catheterized). This was a 54-y/o male with NYHA class III CHF due to ischemic cardiomyopathy and a history of MI, CAD, VT with AICD placement, and diabetes. He was treated for 48 hours with study drug that was discontinued due to clinical improvement. He was discharged on study day 3 but was readmitted on day 15 for worsening CHF and died the same day.

16) Subject # 356-401 (Natrecor adjustable dose, catheterized). This was a 45-y/o male with NYHA class IV CHF due to idiopathic dilated cardiomyopathy and a history of sustained VT (AICD placed), CVA, hypertension and renal insufficiency. He was treated for 24 hours with study drug that was discontinued due to inadequate response. On day 8, the subject's hospitalization was prolonged for pulmonary edema. The subject extubated himself on day 14 and died 45 minutes later.

17) Subject # 369-401 (Natrecor adjustable dose, catheterized). This was a 76-y/o woman with no previous history of CHF and a history of CAD, NSVT, hypertension, diabetes and breast cancer. She presented with shortness of breath. She was treated for 19 hours with study drug. The drug was discontinued due to NSVT that lasted 6 seconds. She had an episode of asymptomatic hypotension that resolved within 10 minutes. About 12 hours she developed a second episode of NSVT. She died on day 12 due to metastatic breast cancer.

18) Subject # 642-406 (Natrecor, adjustable dose, catheterized). This was a 90-y/o male with NYHA class IV CHF due to valvular disease with progressive mitral regurgitation and a history of CAD, CABG, sick sinus syndrome requiring a pacemaker, AF, CRF, abdominal aneurysm and PAT. He was treated for 44 hours with study drug that was discontinued due to inadequate clinical response. He was receiving dobutamine throughout this active drug infusion. On study day # 4, his chest X-ray showed increased fluid retention and possibly pneumonia. His SBP was ~ 50 on day 6 and he was treated with dobutamine and saline. On study day 7 he improved. On day 16 he died due to CHF, severe mitral regurgitation and arteriosclerotic heart disease.

19) Subject # 663-412 (Natrecor, adjustable dose, catheterized). This was an 84-y/o female with NYHA class IV CHF due to ischemic cardiomyopathy and a history of MI, CABG, CAD, atrial fibrillation, VF, sustained VT and hypertension. The subject was treated with 52 hours with study drug that was discontinued due to clinical improvement. The subject was discharged to a nursing home and treated with IV dobutamine on day 8. She died on day 26.

20) Subject # #678-402 (Natrecor, adjustable dose, catheterized). This was an 80-y/o female with NYHA class III CHF due to ischemic cardiomyopathy and mitral regurgitation, CAD, MI, CABG, chronic stable angina and a pacemaker. She was treated for approximately 11 hours with study drug that was discontinued due to chest pain. At that point she withdrew consent. She was placed on a morphine drip. On day 4 the subject died of mitral regurgitation and CAD.

21) Subject # 687-425 (Natrecor adjustable dose, catheterized), This was a 62-y/o male with no previous history of CHF but a history of CAD, non-Q wave MI, CABG, AFl, SVT, hypertension, NIDDM, and treated bowel lymphoma. He was admitted secondary to hypoxia and bacterial endocarditis. The subject's creatinine was 3.6 upon entry into the study. He was treated with NTG, Betapace, digoxin, aspirin, packed RBC and antibiotics. His condition did not improve. His PCWP decreased on study drug from 40 to 24 mm Hg. He had mild bradycardia (HR=62) and severe hypoxia requiring intubation. On day 3, his condition deteriorated and he was sent for surgery. NTG was stared. He was ventilator dependent. On day 20 he died of encephalopathy secondary to the endocarditis.

22) Subject # 688-401 (Natrecor, adjustable dose, catheterized). This was a 74-y/o male with NYAH class IV CHF due to ischemic cardiomyopathy and a history of CRF, DM, CAD, CABG and atrial fibrillation, sinus bradycardia with first degree heart block and COPD. He was treated for 55 hours with study drug but was discontinued due to clinical improvement. On day 4 his creatinine worsened to 4.2 mg/dL. He died on day 12 due to end-stage CHF.

Serious Adverse Events: There were a total of 113 subjects who had serious events that did not lead to death but either led to hospitalization or prolonged an ongoing hospitalization. Fifty-one of these were in the dobutamine groups and 62 among those treated with all regimens of Natrecor.

Nitroglycerin subjects:

1) Subject # 357-506 (PBO/NTG, not catheterized). (49y/o, M, NYHA IV). This subject was readmitted on day 28 due to CHF and was found fluid overloaded. He was treated with dopamine IV Lasix and Zaroxolyn and discharged on day 31.

2) Subject # 369-501 (PBO/NTG, not catheterized) (68 y/o F, NYHA III). This subject's hospitalization was prolonged for a psoas abscess on study day 7. The abscess was drained and the subject received prolonged antibiotic treatment. Her cardiopulmonary status was also compromised, suffering worsening CHF and was treated with IV NTG, milrinone and Lasix. She underwent mitral valve repair one week later.

3) Subject # 369-505 (NTG, not catheterized) (33 y/o F, NYHA III). Hospitalized for abdominal pain from day 11-15 and was discharged on Prevacid and Maalox.

4) Subject #369-507 (PBO/NTG, catheterized) (72y/o M, NYHA III). This patient was readmitted on day 12 for worsening CHF and was treated with IV Lasix, dobutamine, Zaroxyln and Monopril. He was discharged on day 18 but readmitted on day 26. He had a GI bleed requiring transfusion and acid pump inhibitors. He was discharged on day 28.

5) Subject # 382-405 (NTG, catheterized) (79 y/o M, NYHA IV). On day 5 while in hospital and on dobutamine after study drug was discontinued he suffered a cardiac arrest. He was resuscitated. He had a second episode of VT, requiring resuscitation on day #9. He was started on Mexitil. His renal function deteriorated and he was dialyzed. He had a Perma Cath inserted and received intermittent dialysis.

6) Subject #502-403 (NTG, catheterized)(63 y/o M, NYHA II). His baseline creatinine was 4.0 mg/dL. The subject completed 48 hours of study and discontinued for clinical improvement. On day 26 the subject was readmitted for dialysis, creatinine at the time was 6.8 mg/dL. He was discharged to an outpatient hemodialysis unit.

7) Subject # 502-502 (PBO/NTG, not catheterized) (89 y/o M, NYHA IV). He was admitted on day 10 for severe weakness. He was in renal failure with a creatinine of 5.4 mg/dL (no change from baseline). He was discharged on day 22 after dialysis. He was readmitted on day 27 for shortness of breath and pulmonary edema secondary to fluid overload and insufficient dialysis. He was discharged on day 29.

8) Subject # 502-504 (NTG, not catheterized) (73y/o F, NYHA IV). She was admitted on day 21 for AF (HR=135), vomiting, dehydration and hypokalemia. She was discharged on day 29.

9) Subject # 502-507 (PBO/NTG, not catheterized) (69 y/o F, NYHA IV). This subject had an episode of hypotension during the study drug infusion. She was started on dobutamine. On day 2 she developed chest pain that was associated with elevated CK-MB (20.8 ng/ml) consistent with a diagnosis of non-Q wave MI. She was discharged on day 6.

10) Subject 502-209 (PBO/NTG, not catheterized) (77 y/o M, NYHA IV). He was discontinued for inadequate clinical response. He was readmitted to the hospital on day 19 for pneumonia. Two transbronchial lung biopsies demonstrated interstitial fibrosis. He had a GI bleed during the hospital stay. He died on day 47 (after the 30-day observation period) due to idiopathic pneumonitis.

11) Subject # 516-501 (NTG, not catheterized) (64 y/o M, NYHA III). He was treated for 48 hours with improvement. At the time of admission he had a non-Q Wave infarction. On day 6 he had pain in the left leg and fever. On day 35 post-study, he underwent an above the knee amputation due to gangrenous left foot.

12) Subject # 516-502 (NTG, not catheterized) (60 y/o M, NYHA IV). He was treated for 65 hours with discontinuation due to clinical improvement. Labile glucose control was observed during hospitalization. He was to be discharged but developed VT that caused discharge of his defibrillator. Amiodarone was started. On day 10 his renal failure worsened. (Baseline serum creatinine was 2.2 mg/dL, Bun 56 mg/dL; 19 hours post-infusion creatinine was 1.9 mg/dL and BUN was 24 mg/dL). On day 10 the creatinine the creatinine was 3.0 and the BUN was 77. He was discharged on day 26 but readmitted on day 26 for exacerbation of CHF and a UTI. The subject was treated with inotropes and IV antibiotics and discharged on day 30.

13) Subject # 516-503 (NTG, not catheterized)(62 y/o F, NYHA IV). She was successfully treated with study drug for 60 hours. She was readmitted on day 13 for exacerbation of CHF and discharged on day 16.

14) Subject # 524-503 (NTG, not catheterized) (57 y/o F, NYHA I). Successfully completed infusion for 43 hours. She was readmitted on day 16 for dehydration and renal insufficiency. Creatinine was 4.2 mg/dL, BUN was 127 mg/dL and K+ was 5.8 mmol/L. She was treated with IV fluids and Kayexalate. She was discharged on day 20 with a creatinine of 3.0 mg/dL, BUN mg/dL, and K+ 4.7 mmol/L. Baseline values were creatinine 2.4 mg/dL, BUN 68 mg/dL.

15) Subject # 538-404 (NTG, catheterized) (79 y/o F, NYHA I). She was discontinued from the original infusion due to lack of efficacy after 24 hours. She was started on open-labeled NTG. She was discharged on day 8. She was readmitted on day 30 for renal failure and dehydration. Her creatinine on admission was 4.5 mg/dl and BUN was 108 mg/dL. She was treated with IV fluids and low dose dopamine. Her creatinine and BUN upon discharge on day 35 were 1.9 and 37 mg/dL, respectively.

16) Subject # 538-407 (NTG, catheterized) (59 y/o M, NYHA III). He was successfully treated for the 76 hours of the initial infusion and discharged on day 8. He was readmitted on day 9 for cellulitis of the lower leg and was treated with IV antibiotics. He developed progressive azotemia on day 11 (with a creatinine of 5.8 mg/dL and BUN 157 mg/dL and a K+ of 7.4 mmol/L. Baseline creatinine was 2.0 mg/dl. The subject was hemodialyzed and was discharged on day 20. (did the subject need more than one dialysis?).

17) Subject # 540-401 (NTG, catheterized)(64 y/o M, NYHA II). He was treated 24 hours with study drug with minimal improvement. He had a cardiac transplant and was discharged on day 17. He was re-hospitalized on day 20 with a low-grade fever, diarrhea, rash, nausea and vomiting. A cardiac biopsy ruled out ejection. He was treated with Flagyl and IV fluids and the diarrhea resolved. He was discharged on day 23.

18) Subject # 540-501 (NTG, not catheterized) (57y/o F, NYHA II). She completed 48 hours of infusion with the infusion discontinued due to lack of efficacy. She was discharged on day 4. The subject was readmitted on day 13 for worsening heart failure and was treated with milrinone. She improved and was discharged on day 16.

19) Subject # 543-404 (NTG, not catheterized). (57 y/o M, NYHA IV). He was post open-heart surgery at the time of enrollment of the study and was on dobutamine at baseline with the inotrope continued throughout the infusion. The subject was treated for 24 hours with study infusion that was discontinued due to lack of efficacy. The subject's hospitalization was prolonged due to worsening decompensated CHF, acute renal failure and staphylococcal bacteremia. An intra-aortic balloon pump was inserted. The subject progressed to pre-renal azotemia and hyponatremia and was dialyzed. The subject's heart failure did not improve and the subject died on day 38 (post 30-day observation period).

20) Subject # 547-502 (PBO/NTG, not catheterized) (94 y/o M, NYHA II). Study drug administered for 24 hours and stopped due to improvement. He had one episode of asymptotic hypotension during the infusion. The subject's hospitalization was prolonged due to CHF exacerbation. The subject was treated with Lasix and dopamine, and discharged on study day 18.

21) Subject # 554-406 (PBO/NTG, catheterized)(58 y/o M, NYHA IV), The subject successfully completed 25 hours of infusion. He was discharged on day 7 and readmitted on day 13 for exacerbation of CHF. He was discharged on day 21.

22) Subject # 554-417 (NTG, catheterized) (44 y/o M, NYHA III). This subject successfully completed a 28-hour infusion. He was discharged on study day 9. On day 25, he was readmitted due to pulmonary edema. He was discharged on day 28.

23) Subject # 554-421 (NTG, catheterized)(62 y/o M, NYHA IV). This subject was treated successfully with study drug for 25 hours. The subject was discharged on day 5 but readmitted on day 19 due to worsening heart failure. He was treated with IV Lasix and discharged on day 24. He was re-hospitalized on day 27 for worsening heart failure. He was treated with inotropes and underwent a heart transplant. The inotropes were continued. He was discharged on day 75. The post-transplant course was complicated by right putaminal hemorrhage with subarachnoid bleeding, pulmonary hypertension, right ventricular dysfunction and acute renal failure.

24) Subject # 554-513 (NTG, not catheterized) (53 y/o F, NYHA IV). The subject was discontinued after 45 hours of study drug infusion due to clinical improvement. The subject was discharged on day 18 and was readmitted on day 23 for worsening heart failure. She was treated with IV Lasix. She developed GE reflux. She was discharged on day 51.

25) Subject # 554-527 (NTG, not catheterized) (57 y/o F, NYHA III). She was treated successfully with study drug for 24-hours. The subject was discharged on day 3 and subsequently developed a right-sided hemiparesis and was readmitted on day 10. Brain MRI revealed an old thalamic stroke.

26) Subject # 554-528 (NTG, not catheterized) (55 y/o F, NYHA IV). She received study infusion that was discontinued due to improvement. She was discharged on day 5 but readmitted on day 8 for pneumonia. She was ventilated on day 10. Post-extubation she had vocal cord paralysis and a depressed gag reflex. She developed severe diarrhea after the initiation of tube feeding. She was discharged to a nursing home at day 54 post-infusion.

27) Subject # 554-532 (PBO/NTG, not catheterized) (41 y/o M, NYHA III). This subject was successfully treated with study drug infusion for 29 hours. He was discharged on day 3. On study day 21 he was admitted for worsening CHF and chest pain. MI was ruled out. He was discharged on day 23.

28) Subject # 561-501 (NTG, not catheterized)(66 y/o F, NYHA I). She was enrolled immediately post Q-wave MI and was stented prior to entered in the study. The attending physician stopped the infusion after the subject received 16 hours of study drug. The subject had an episode of asymptotic hypotension that lasted 1.5 hours with interruption of the infusion for 1.5 hours. On day 4 she complained of chest pain with ECG consistent with MI. A PTCA was subsequently performed. She was discharged on day 19. She was readmitted on day 20 for chest pain with a negative troponin. She was discharged on day 23

29) Subject # 572-408 (NTG, catheterized) (21 y/o M, NYHA III). This subject was treated with infusion for 48 hours with study drug discontinued due to lack of efficacy. He was discharged on day 7, but readmitted on day 14 with a 6.8-kg weight gain and shortness of breath. He was treated with IV Lasix, and discharged home on day 15.

30) Subject # 572-504 (NTG, not catheterized). (72 y/o M, NYHA III). He was initially treated for 25 hours with the infusion successfully completed. He was discharged on day 3. On study day 14 he was readmitted for worsening heart failure and was treated under Swan Ganz monitoring with IV NTG. He had AF and was cardioverted. He also had a rectus sheath hematoma. He was discharged on day 31.

31) Subject #580-402 (NTG, catheterized) (52 y/o M, NYHA IV). Treated for 24 hours with study drug that was stopped because of clinical improvement. He was discharged on day 3 and readmitted on day 7 for pneumonia. He was treated with antibiotics and discharged on day 17. He was readmitted on day 25 for decompensated CHF. He was diuresed and received inotropic support. There was some decrease in his renal function. His admission creatinine was 1.6 mg/dL; his discharge creatinine was 1.9 mg/dL. He also had a right lower extremity ulcer for which he received antibiotic treatment. He was discharged on day 37.

32) Subject # 580-411 (NTG, catheterized) (75 y/o M, NYHA IV). He was treated for 24 hours with study drug. The drug was discontinued because of clinical improvement. He was discharged on day 6 but readmitted on day 22 worsening CHF and elevated LFTs. He was treated with inotropic drug and discharged on day 32.

33) Subject # 580-504 (NTG, not catheterized) (43 y/o M, NYHA IV). He was treated with study drug for 2 days and discontinued due to clinical improvement. The subjects hospitalization was prolonged due to elevated liver enzymes (the subject had a history of hepatitis C). He was discharged on day 5 to hospice care. He was readmitted on study day 28 for recurrent hemoptysis, increased dyspnea, fatigue, malaise and edema. He was diagnosed with volume overload and treated with diuretics and antibiotics. He was discharged on day30.

34) Subject #585-502 (NTG, not catheterized) (67 y/o M, NYHA IV). He had limited response to infusion during the 24-hour infusion. On day 1 an echocardiogram showed a dehiscence of the mitral annuloplasty ring, which was the apparent cause of the CHF decompensation. On day 7 he had a mitral valve replacement. An intra-aortic balloon pump was placed. On day 8 he experienced respiratory failure and cardiogenic shock. He was mechanically ventilated. He was transfused. He also had worsening renal failure and was treated Lasix, dopamine, epinephrine, heparin and dobutamine. He had a Quinton catheter placed for continuous veno-venous hemo-filtration. These events reversed on

day 11 with veno-venous filtration continuing till day 12 and the aortic pump till day 13. He was extubated on day 14. No discharge date was supplied.

35) Subject # 627-402 (NTG, catheterized) (72 y/o M, NYHA III). He was treated for 37 hours and the infusion stopped due to clinical improvement. He was discharged on day 6 but readmitted on day 18 due to worsening renal failure. He was treated with renal dose dopamine, Kayexalate, bicarbonate, Lanoxin, albuterol and fluids and transferred to a tertiary care hospital.

36) Subject # 628-401 9NTG, catheterized) (53 y/o M, NYHA IV). He was treated for 48 hours with study drug that was discontinued due to clinical improvement. He was treated with dobutamine on day 3 (post-study drug) and started on milrinone on day 4. He was discharged on day 7. He was readmitted on day 8 for unstable angina and was treated with milrinone, IV NTG and heparin. No MI was found. He was discharged on day 13. On day 14 he was readmitted with chest pain nausea, vomiting and diarrhea. No MI was found. He was discharged on day 43.

37) Subject # 636-501 (NTG, not catheterized) (38 y/o M, NYHA IV). Treated for 3 days with study drug that was discontinued due to lack of efficacy. He was discharged on day12 and readmitted on day 30 for chest pain and shortness of breath. He was discharged the next day after receiving IV Lasix.

38) Subject # 642-204 (NTG, catheterized) (65 y/o M, NYHA III). He was treated for 24 hours with study drug that was discontinued due to clinical improvement. He was discharged on day 11 and readmitted on day 17 because of bladder outlet obstruction. He had a transurethral resection of the prostate performed. He was discharged on day 28 but readmitted on day 30 because of chest pain. An acute MI was ruled out and he was discharged on day 31.

39) Subject # 657-501 (PBO/NTG, not catheterized) (76 y/o M, NYHA I). He was admitted initially due to inferior MI and severe pulmonary edema. He received study drug for 28 hours, which was discontinued to receive open label NTG in preparation for CABG. An intra-aortic balloon pump and Swan-Ganz catheter was placed. He had 4-vessel bypass and mitral valve replacement. Post-operative complications included cardiogenic shock, respiratory insufficiency, renal insufficiency and acute pancreatitis. He was extubated on day 45 and discharged on day 54.

40) Subject # 663-45 (NTG, catheterized) (75 y/o M, NYHA II). He was admitted with an acute MI and received study drug for 24 hours. Dopamine was added after five hours of infusion. He was discharged on day 14. On study day 19, he was readmitted for CHF, AF and pleural effusion. He was treated with Lasix and discharged on day 21. He was readmitted on day 23 and treated for exacerbations of CHF and received diuretics and inotropes. He was discharged on day 30.

41) Subject # 663-406 (NTG, catheterized) (41 y/o M, NYHA I). He was admitted for an acute anterior wall MI and CHF. Post-MI, he had severe triple vessel disease and an ejection fraction of 10%. He had a quadruple vessel CABG. Acute renal failure and CHF complicated his post-operative course. He was treated with study drug 13 days after the index MI and the treated for 24 hours with clinical improvement. He was discharged 6 days later. He was readmitted on day 26 (post study drug) due to CHF exacerbation, treated with Lasix and dobutamine and discharged on day 30.

42) Subject # 663-508 (PBO/NTG, not catheterized) (83 y/o F, NYHA I). She was treated successfully for 24 hours and discharged on day 7 but readmitted on day 8 for dehydration and dyspnea. She was discharged on day 13.

43) Subject # 667-406 (PBO/NTG, catheterized) (32 y/o M, NYHA IV). He was treated 3 days with study drug that was discontinued due to clinical improvement. He had a history of CRF. On day 5, he had a CAPD catheter placed and dialysis was initiated on day 16. His creatinine was 2.8 at baseline and 2.9 mg/dL at the time of dialysis catheter placement. He was discharged on day 16 but readmitted on day 25 due to exacerbation of CHF and repair of the dialysis catheter. He was treated with IV diuretics, inotropes and after load reducers. His course was complicated by the need for a Quinton catheter. He also had cellulitis of the lower legs and 2-lumen Hickman catheter placement (for hemodialysis, the CAPD catheter was malfunctioning). He was discharged on day 38.

44) Subject # 667-412 (NTG, catheterized) (53 y/o M, NYHA III). He was treated with study drug for 24- hours that were discontinued due to clinical improvement. He was rehospitalized on day 26 for CHF exacerbation. No additional details were available.

45) Subject # 671-501 (PBO/NTG, not catheterized) (83 y/o M, NYHA IV). He was treated for 24 hours with study drug that was discontinued due to improvement. He was discharged on day 4, but readmitted on day 15 for CHF exacerbation. He was discharged on day 19.

46) Subject # 671-508 (NTG, not catheterized) (65 y/o M, NYHA IV). He was treated for 24 hours with drug that was discontinued due to lack of efficacy. He was discharged on day 5 but readmitted on day 16 for worsening CHF. He was treated and discharged on day 19.

47) Subject # 678-508 (NTG, not catheterized) (67 y/o M, NYHA III). He was treated for 24 hours with study drug that was discontinued due to clinical improvement. He was discharged on day 2 but readmitted on day 20 after a respiratory arrest post-pacemaker placement. The subject died on day 36 (after the 30-day cutoff).

48) Subject # 678-510 (NTG, not catheterized) (77 y/o NYHA IV). He was treated for 24 hours with study drug that was discontinued due to clinical improvement. He was discharged on day 3 but readmitted on day 11 for worsening CHF. He was discharged on day 15 but readmitted again on day 22 for pneumonia and worsening CHF. He was treated and discharged on day 30.

49) Subject # 681-403 (NTG, catheterized) (44 y/o F, NYHA III). She was treated with study drug for 24 hours that was discontinued due to clinical improvement. She was discharged on day 2, but readmitted on day 21 for exacerbation of CHF with fluid overload. She was treated with IV diuretics and milrinone and discharged on day 29.

50) Subject # 683-401 (NTG, catheterized) (51 y/o F, NYHA IV). She was treated for 48-hours that was discontinued due to lack of efficacy. She was subsequently given IV Lasix and dopamine. She experienced symptomatic hypotension at that time. Both study drug and dopamine were discontinued. She was discharged on study day 9 with home milrinone therapy. She was readmitted on day 27 for treatment of a left pneumothorax after Broviac placement. She had a chest tube and a Broviac placed. She was discharged on day 28.

51) Subject # 687-421 (PBO/NTG, catheterized) (79 y/o F, NYHA III). She was treated with study drug for 48 hours with the drug stopped because of lack of efficacy. She was discharged on day 6 but readmitted on day 21 for nausea, vomiting and dehydration. She was treated with fluids and her medications adjusted. She was discharged on day 25.

NATRECOR SUBJECTS:

1) Subject # 360-501 (NAT fixed dose, not catheterized) (48 y/o M, NYHA IV). He was treated for 24 hours and the infusion discontinued due to clinical improvement. He was discharged on day 4 but readmitted on day 24 for CHF exacerbation. He was diuresed and discharged on day 27.

2) Subject # 367-401 (PBO/NAT fixed dose. catheterized) (71 y/o M, NYHA IV). He was treated for 24 hours with the infusion discontinued due to inadequate clinical response. He arrested on day 22, while being evaluated for a heart transplant. He was reintubated and treated with IV fluids and discharged on day 30.

3) Subject # 369-411 (PBO/NAT, fixed dose) (68 /o M, NYHA III). He was treated for 24 hours with study drug with the infusion stopped due to clinical improvement. He was discharged on day 15. He was readmitted on day 26 for left epigastric pain. A MI was ruled out.

4) Subject # 369-416 (PBO/NAT, fixed dose, catheterized)(73y/o F, NYHA III), Treated with study drug for 24 hours with the drug discontinued due to clinical efficacy. She was discharged on day 11 but readmitted on day 12 due to shortness of breath and blisters on her BKA amputations. She was treated with oxygen and milrinone and discharged on day 32.

5) Subject # 369-420 (NA fixed dose, catheterized) (57 y/o M NYHA III). He was treated for 24 hours and discontinued due to clinical improvement. He was discharged on day 8 but readmitted on day 26 due to CHF exacerbation, hyperkalemia and renal insufficiency (he did not have renal insufficiency at baseline). He also developed short runs of VT and PVCs. He was discharged on day 35.

6) Subject # 369-514 (NAT fixed dose, not catheterized) (78 y/o M, NYHA III). He was treated with study drug for 4 days, which was discontinued due to lack of efficacy. On day 7, his renal failure worsened. Baseline creatinine and BUN were 1.1 and 52 mg/dL, respectively. Hemodialysis was initiated on day 20. He was discharged to a rehabilitation facility on day 30 with three-times a week dialysis.

7) Subject # 369-519 (NAT, fixed dose, not catheterized) (74 y/o F, NYHA III) She was treated for 24 hours with study drug, with drug discontinued due to minimal improvement. She received milrinone. Her hospitalization was prolonged due to episodes of bradycardia. A DDD pacemaker was placed. She was discharged on day 13.

8) Subject # 524-502 (PBO/NAT, fixed dose, not catheterized) (51 y/o M, NYHA III). He was treated for 43 hours with drug discontinued due to withdrawal of consent. On day 18 he was hospitalized for worsening bronchitis. He was treated with antibiotics and corticosteroids. He signed out AMA on day 23.

9) Subject # 554-522 (NAT, fixed dose, not catheterized) (70 y/o F, NYHA IV). She was treated for 24 hours with study during and discontinued due to clinical improvement. She was discharged on day 18, but readmitted on day 22 due to worsening CHF and atrial fibrillation. She was treated with digoxin and Lasix and discharged on day 27.

10) Subject # 554-524 (NAT, fixed dose, not catheterized) (63 y/o F, NYHA IV). She was treated for 24 hours and the infusion stopped due to clinical improvement. She was readmitted on day 14 with CHF exacerbation and was treated with benazapril, digoxin and Lasix. A thoracocentesis was performed and was discharged on day 22. She was readmitted on day 29, again for CHF exacerbation and was discharged on day 44.

11) Subject # 554-545 (NAT, fixed dose, not catheterized) (79 y/o F, NYHA II). She was treated with study drug infusion for 24 hours and the infusion stopped because of clinical improvement. She had baseline renal dysfunction (BUN- 63, creatinine –3.5 mg/dL). On day 5 her renal function deteriorated (BUN=98, Creatinine =6.0 mg/dL). Hemodialysis was started on day 5. She had a non-Q wave infarction on day 7. She underwent a PTCA on day 26. She was discharged on day 53 still requiring intermittent hemodialysis.

12) Subject # 560-401 (NAT, fixed dose, catheterized) (68 y/o M, NYHA IV). He was infused for 24 hours, with the infusion stopped due to clinical improvement. He was discharged on day 11 and admitted on day 26 for worsening CHF. He was treated with Lasix and milrinone and discharged on day 29.

13) Subject # 560-402 (NAT, fixed dose, catheterized) (63 y/o M, NYHA II). He was treated for 24 hours, with the infusion discontinued due to clinical improvement. On day 4, he had an episode of VT and required intubation and treatment of dopamine, amiodarone and lidocaine and an intra-aortic balloon pump was inserted. He had heart transplant surgery on day 11.

14) Subject # 561-503 (NAT, fixed dose, not catheterized) (54 y/o F, NYHA IV). She was treated with study drug for 48 hours, with the drug discontinued due to clinical improvement. She was discharged on day 6, but readmitted on day 21 for recurrent CHF and possible pyelonephritis. Her renal insufficiency worsened (creatinine peak =4.0 mg/dL; baseline =2.2 mg/dL). She was diagnosed with ATN. She was treated with IV Lasix and her CHF improved. Atrial fibrillation, a foot ulcer and a possible urinary tract infection also complicated her hospitalization. She was discharged on day 27.

15) Subject # 572-414 (NAT, fixed dose catheterized). (64 y/o M, NYHA Class III). He was treated for 49 hours with study drug with the infusion stopped due to lack of improvement. Dobutamine was added. On day 5, hospitalization was prolonged due to worsening heart failure. The subject also received milrinone for 6 weeks followed by ongoing nitroprusside and dobutamine till study day 60. As of study day 7, he was placed on a transplant list.

16) Subject # 572-420 (PBO.NAT, fixed dose, catheterized) (64 y/o F, NYHA III). He was treated with study drug for 27 hours when the infusion was discontinued due to clinical improvement. She was discharged on day 7 and readmitted on 28 due to right upper abdominal burning and pain. Renal ultrasound showed compromised blood flow to both kidneys. An HIDA scan showed chronic cholecystits. She was treated with metronidazole and ciprofloxacin and discharged on day 36.

17) Subject # 572-501 (NAT, fixed dose, not catheterized) (71 y/o M, NYHA III). He was treated with study drug for 48 clinical improvement. After 6 hours of therapy, he was treated for hyperkalemia (K=5.4, baseline 5.1 meq/L). There was no history of baseline renal dysfunction. He also had PVCs. He was discharged on day 4, and readmitted on day 22 with a K= of 6.7 meq/L. He was treated with Kayexalate and spironolactone.

18) Subject # 572-502 (NAT, fixed dose, not catheterized)(80 y/o M, NYHA IV). The study drug was infused for 27 hours and discontinued due to lack of clinical improvement. Dobutamine was added on study day 1 and switched to milrinone after study drug was discontinued. He was discharged on day 6, but readmitted on day 11 for worsening heart failure due to fluid overload and worsening renal failure (creatinine =5.1 mg/dL, baseline 2.9 mg/dL). He was treated with antibiotics and discharged on day 22 with a creatinine of 5.3 mg/dL.

19) Subject # 580-403 (PBO/NAT fixed dose, catheterized)(50 y/o M, NYHA IV). He was treated for 48 hours with drug that was discontinued due to clinical improvement. He was discharged after day 3 but readmitted on day 7 for dehydration and symptomatic hypotension. He was treated with dobutamine and fluid. Relative to baseline his renal function deteriorated (creatinine = 3.4 mg/dL; baseline 1.9 mg/dL). His renal function improved with hydration. His hospital course was complicated by fluid overload. He was diuresed and discharged on day 11.

20) Subject # 580-409 (NAT, fixed dose, catheterized) (69 y/o M, NYHA IV). He was treated with study drug for 24-hours that was stopped due to clinical improvement. He was discharged on day 3, but readmitted on day 7 with symptoms of hypotension, dehydration, abdominal pain and vomiting. Digoxin toxicity was diagnosed. His hospitalization was prolonged due to asymptomatic bradycardia. His amiodarone and digoxin were discontinued. He was discharged on study day 13.

21) Subject # 585-401 (NAT, fixed dose, catheterized) (64 y/o M, NYHA IV). This subject was treated for 24 hours of infusion with the infusion discontinued due to lack of clinical response. He was subsequently treated with dobutamine. He was discharged on day 4, but readmitted on day 25 due to dehydration, fever and hypotension (84/54 mm Hg). Carvedolol and Lasix were withheld. He subsequently was found to have a foot ulcer, a blood culture was positive. He was treated with antibiotics and discharged on day 32.

22) Subject # 605-505 (PBO/NAT, fixed dose, not catheterized). (68 y/o M, NYHA I). This subject was treated for 24 hours with study drug that was discontinued due to clinical improvement. On day 5 he was diagnosed with ARDS and was intubated. He was extubated and discharged on day 20.

23) Subject # 605-508 (NAT, fixed dose, not catheterized) (57y/o M, NYHA III). IV dobutamine was added to study drug 2 hours after the start of the infusion to increase cardiac output. Study drug was discontinued due to clinical improvement but IV dopamine was initiated. The subject had a history of chronic renal insufficiency. He had a catheter placed for dialysis and hemodialysis was initiated on day 16. He was discharged on day 18.

24) Subject # 627-502 (PBO/NAT, fixed dose, not catheterized)(74 y/o M, NYHA class I). His study drug was discontinued at day 3, due to worsening renal failure. His creatinine increased from a baseline value of 3.9 to 5.6 mg/dL. A permanent catheter was placed. Two days later he was intubated due to respiratory acidosis. He was discharged on day 40.

25) Subject # 627-510 (PBO/NAT, fixed dose, not catheterized) (78 y/o M. NYHA III) He was treated with study drug for 48 hour with the infusion discontinued due to clinical improvement. He was discharged on study day 3, but readmitted on day 7 for CHF and chest pain. He was hypertensive and tachycardic, cardiac enzymes were normal. He had a cardiac catheterization, which showed total occluded proximal left anterior descending artery and a sub-total proximal left circumflex and mid-right coronary artery. His creatinine increased from 2.0 a baseline to 2.5 mg/dL. A renal scan showed no visualization of the left kidney and poor cortical transit within the right kidney. A renal arteriogram showed an occluded left renal artery. He was discharged on study day 12 with a creatinine of 2.4 mg/dL.

26) Subject # 636-401 (NAT, fixed dose, catheterized) (46 y/o F, NYHA IV). She was treated for 56 hours and discontinued due to clinical improvement. She was discharged on day 6 and readmitted on day 9 due to dehydration and fatigue, lightheadedness, nausea and diarrhea. She was treated with IV fluids while diuretics were withheld. She was discharged on day 13.

27) Subject # 636-502(NAT, fixed dose, not catheterized)(56 y/o M, NYHA not stated). This was a subject with progressive cardiomyopathy, s/p mitral valve replacement (secondary to rheumatic heart disease) and AICD placement. He was on a cardiac transplant list with seven in subject admissions for CHF. The subject was maintained on NAT till transplanted on day 161. Post transplant he required high doses of inotropic support and an intra-aortic balloon pump was placed. Two days post transplant he developed right ventricular failure, oliguria, hyperkalemia and eventually left ventricular failure. He died of multi-organ failure 3 days later (day 164, i.e. post 30-day cut-off).

28) Subject # 636-504 (PBO/NAT fixed dose, not catheterized) (59y/o M, NYHA IV). This subject was treated for 48 hours with study drug that was discontinued due to clinical improvement. He was discharged on day 12. At that time his creatinine was 2.1 mg/dl (baseline was ???). He was readmitted on study day 15 with large-volume watery diarrhea, acute renal failure (serum creatinine 4.1 mg/dL), hyperkalemia (6.9 meq/L) and hypotension (68/43 mm Hg). He was discharged on study day 22. On study day 26 he was readmitted with CHF, increasing diarrhea, malaise, dyspnea and chest pain. His creatinine was 2.0 mg/dL. He received IV furosemide and dobutamine with minimal improvement. He was discharged to home for hospice care on study day 36. He died on day 48 (post-30 day cut-off).

29) Subject # 638-501 (NAT, fixed dose, not catheterized) (71 y/o M, NYHA III). This subject was treated for 68 hours with study drug with clinical improvement. He was discharged on day 6, but readmitted on day 11 for dehydration, CHF and hyponatremia. He had weight loss, cachexia and poor appetite. He was placed on a DO NOT RESUSCITATE status and the defibrillator was turned off. The subject was alive at day 32.

30) Subject # 638-504 (NAT, fixed dose, not catheterized) (85 y/o M, NYHA IV). He was treated with study drug that was discontinued due to clinical improvement. He was discharged on day 5, but readmitted on day 25 because of nausea, vomiting and diarrhea. He was treated with IV fluids Pepcid, Regalin and Lomotil. He was discharged on day 28.

31) Subject # 642-403 (NAT, fixed dose, catheterized) (85 y/o F, NYHA III). She was treated for 24 hours with discontinuation due to clinical improvement. She was readmitted on day 15 for a UTI, treated and discharged the next day.

32) Subject # 642-504 (NAT, fixed dose, not catheterized) (56 y/o F, NYHA I). She was treated for 45 hours with the drug discontinued due to lack of efficacy. She was readmitted on day 16 due to worsening CHF, weight gain and abdominal distention. Her CHF symptoms resolved with diuretics and she was discharged on day 19.

33) Subject #663-511 (NAT, fixed dose, not catheterized) (60 y/o M, NYHA I). He was treated for 24-hours with study drug with infusion stopped due to unwillingness to continue. He was readmitted on day 14 due to change in mental status. No diagnosis was made. The subject was discharged on day 21.

34) Subjects # 667-403 (NAT, fixed dose, catheterized) (50 y/o M NYHA IV). He was treated for 39 hours with the infusion stopped for clinical improvement. On day 10, he experienced an episode of symptomatic hypotension with SBP falling to 60 mm Hg. He was treated with dobutamine and dopamine. His symptoms resolved in 3 hours.

35) Subject # 667-425 (NAT, fixed dose, catheterized)(66 y/o M, NYHA III). He was treated for 24 hours, with the infusion stopped because of clinical improvement. His hospitalization was prolonged due to worsening renal function, with a creatinine of 3.2 mg/dL (baseline creatinine 1.4 mg/L). He was transferred to the ICU (creatinine 4.4 mg/dL). His creatinine peaked at 7.5 mg/dL on study day 18. He was treated with renal doses of dopamine. He was discharged on day 30 with a creatinine of 2.4 mg/dL.

36) Subject # 671-401 (PBO/NAT, fixed dose, catheterized) (78 y/o F, NYHA IV). She was treated with study drug for 48 hours for clinical improvement. On study day 4, she experienced symptomatic hypotension that lasted 20 minutes and a second episode on day 7 that lasted 70 minutes. She was readmitted to the hospital on day 21 due to a GI bleed. Her Hgb was 8.7 g/L. She received 2 units of PRBC. She was discharged to a nursing home on day 26.

37) Subject # 674-501 (PBO/NAT, fixed dose, not catheterized) (55 y/o F, NYHA IV). She was treated for 24 hours, with the drug discontinued due to clinical improvement. She was readmitted to the hospital on day 12 for respiratory distress and epilepsy (there was a history of seizure disorder). She was intubated and given lidocaine. She was

discharged on day 16 and readmitted on day 22 for anemia that included a bone marrow. She was discharged on study day 27.

38) Subject # 677-501 (NAT, fixed dose, not catheterized) (75 y/o F, NYHA IV). She was treated for three days with the infusion discontinued due to clinical improvement. She was discharged on day 6 but readmitted on day 8 due to worsening heart failure, She was treated with diuretics and discharged on day 12.

39) Subject # 677-503 (PBO/NAT, fixed dose, not catheterized) (80 y/o M, NYHA IV). This subject was treated for 24 hours, with the infusion stopped for clinical improvement. He developed sepsis and treated with antibiotics. He was discharged on day 11.

40) Subject # 677-504(NAT, fixed dose, not catheterized) (43 y/o M. NYHA III). He was treated for 15 days and discontinued due to clinical improvement. He was readmitted on day 25 for hyperglycemia (there was a baseline history of diabetes) and chest pain. He was discharged on day 30.

41) Subject # 678-404 (NAT, fixed dose, catheterized) (58 y/o M, NYHA III). He was treated for 4 days, with the infusion stopped due to inadequate clinical response. He had worsening heart failure on day 9 that prolonged his hospitalization. He did not respond to IV inotrope or diuretic therapy. He was placed on a cardiac transplantation list a left ventricular assist device was inserted on day 30. The subject had cardiac tamponade on day 31 and died.

42) Subject # 678-501 (NAT, fixed dose, not catheterized) (75 y/o M, NYHA IV). He was treated with study drug which was discontinued due to clinical improvement. He was discharged on day 4 but readmitted on day 6 for CHF exacerbation and AF with a rapid ventricular response. He was treated with dobutamine and Cardiazem and discharged on day 16.

43) Subject # 678-502 (PBO/NAT, fixed dose, not catheterized) (86 y/o F, NYHA IV). She was treated with study drug with clinical improvement. Dobutamine was initiated after study drug was discontinued. Hospitalization was prolonged for dialysis access. She had baseline CRF (baseline creatinine was 5.3 mg/dl). She had a Tenckhoff catheter placed and developed fever and abdominal cramping. Peritoneal dialysis was started on day 13. She was discharged with chronic dialysis.

44) Subject # 678-513 (NAT, fixed dose, not catheterized). (67 y/o M, NYHA III). The subject was treated for 42 hours with study drug that was discontinued due to clinical improvement. He was discharged on day 4 but readmitted on day 15 due to syncope attributed to atrial arrhythmia (picked up by the AICD). His amiodarone dose was increased. His creatinine worsened post treatment to 3.7 mg/dL (baseline 1.9 mg/dL). He received dobutamine and dopamine for CHF. He died on day 31 (1-day post cut-off).

45) Subject # 679-502 (NAT, fixed dose, not catheterized) (39 y/o M, NYHA III). This subject was treated for 24 hours with the infusion stopped because of clinical improvement. He was discharged on day 2 but readmitted on day 21 due to worsening CHF. A right heart catheter was placed and he was treated with IV Lasix. He was listed for cardiac transplantation.

46) Subject # 681-501 (PBO/NAT, fixed dose, not catheterized) (43 y/o M, NYHA IV). He was treated with study infusion for 24 hours, with the infusion discontinued due to clinical improvement. He was discharged on day 4 but rehospitalized on day 14 for gastroenteritis. He was treated with IV fluid for dehydration. He was hypotensive at the time. He was discharged on study day 15.

47) Subject # 681-506 (NAT, fixed dose, not catheterized) (58 y/o M, NYHA IV). He was treated for 24 hours with the infusion stopped because of clinical improvement. He was discharged on day 4 but rehospitalized on day 15 for evaluation of mental status described as catatonic. He was treated with dobutamine and Lasix (presumably because of worsened heart failure). He was discharged on day 19.

48) Subject # 681-507 (NAT, fixed dose, not catheterized) (68 y/o M, NYHA IV). He was treated for 24 hours, with study drug that was discontinued due to clinical improvement. He was discharged on day 4 but was readmitted on day 21 due to gout. He was treated with intra-articular steroids and discharged on day 25.

49) Subject # 687-401 (NAT, fixed dose, catheterized) (71 y/o M, NYHA IV). He was initially hospitalized for an exacerbation of CHF and was started on study drug thirteen days into the hospitalization. He was treated for 4 days and was discharged 6 days later but readmitted on day 29 for CHF and anemia. He was treated with Lasix, Zaroxolyn, aldactone and milrinone and discharged four days later.

50) Subject # 687-415 (PBO/NAT, fixed dose, catheterized) (69 y/o M, NYHA III). He was treated with study drug for two days. The infusion stopped due to clinical improvement. He had an episode of gastrointestinal bleeding prior to the start of the infusion that required FFP and 5 units of packed red blood cells. He was discharged on day 9 but readmitted on day 13 for rectal bleeding. He was discharged on day 22.

51) Subject # 688-402 (PBO/NAT, fixed dose, catheterized) (40 y/o M. NYHA IV). He was initially admitted for CHF and entered into the study 10 days later. He was treated with drug for 52 hours and discontinued due to lack of clinical response. He had an episode of VT during the infusion that required cardioversion. He was hypotensive with a BP of 72/25 (did this cause the VT or visa versa???). The episode lasted 45 minutes. He was discharged 2 weeks later.

52) Subject # 695-401 (NAT, fixed dose, catheterized) (58 y/o M, NYHA IV). This subject was treated with study drug for 24 hours and discontinued due to clinical response. He developed line sepsis and was treated with antibiotics for 5 days. Hemodialysis was initiated on day 9 because the subject began to hallucinate and was agitated. His psychiatric symptoms as well as leg edema resolved. He was discharged on day 16, no longer requiring dialysis.

53) Subject # 369-419 (Nat, adjustable dose, catheterized) (58 y/o F, NYHA IV). The subject was treated for 24 hours, with study drug discontinued due to clinical improvement. She was discharged on day 8 but readmitted on day 22 for decompensated CHF and evaluation for heart transplant. She was treated with Lasix and milrinone and discharged on day 28.

54) Subject # 519-401 (NAT adjustable dose, catheterized) (67 y/o F, NYHA III). She was treated for 24 hours with the infusion discontinued due to clinical improvement. Her hospitalization was prolonged due to worsening renal function that required dialysis (baseline creatinine/ BUN 2.4/ 69) on treatment creatinine/ BUN (3.3/97 mg/dL). She was discharged on hemodialysis three times a week.

55) Subject # 554-422 (NAT, adjustable dose, catheterized) (74 y/o F, NYHA III). She was treated with infusion for 24 hours and discontinued due to inadequate clinical response. She was discharged on day 4 but was readmitted on day 24 due to fluid overload. She was diuresed with Lasix and discharged on day 26.

56) Subject # 572-409 (NAT, adjustable dose, catheterized) (50 y/o F, NYHA III). She was treated for 24 hours with study drug and discontinued due to inadequate response. Milrinone was initiated after study drug discontinuation. Her hospitalization was prolonged due to episodes of VT on days 20, 23 and 24 which responded either to cardioversion plus lidocaine or amiodarone, lidocaine and adenosine. Her condition deteriorated and a LVAD was inserted as a bridge to cardiac transplant.

57) Subject # 572-417 (NAT adjustable dose, catheterized) (62 y/o M, NYHA III). This subject was treated with study drug for 48 hours and was discontinued due to clinical improvement. He was discharged on day 10 but readmitted on day 18 due to increased PVCs. .He was discharged on day 22.

58) Subject # 572-419 (NAT, adjustable dose, catheterized). (59 y/o M, NYHA IV). He was treated with study drug for 51 hours and discontinued due to clinical improvement. He was discharged on day 6 but readmitted on day 8 for confusion. His baseline creatinine was 1.9 mg/dL. On readmission his creatinine was 4.2 mg/dL. Diuretics were withheld and creatinine levels reapproached baseline. He was treated with milrinone and NTG for CHF exacerbation. He was discharged on day 35.

59) Subject # 620-401 (NAT, adjustable dose, catheterized) (60 y/o M, NYHA III). He was treated for 24 hours with the infusion stopped due to clinical improvement. He experienced a non-Q wave MI on day 6. He was discharged on day 12 but readmitted on day 21 due to increasing CHF symptoms and worsening peripheral edema and elevated creatinine (3.1 mg/dL; baseline 1.8 mg/dL). His creatinine returned to baseline and he was discharged on day 26.

60) Subject # 667-408 (NAT, adjustable dose, catheterized)(55 y/o M. NYHA III). He was treated for 18 hours with the infusion discontinued due to clinical improvement. On day 8 his CHF status worsened and he was sent back to the ICU for Swan Ganz placement and milrinone treatment. He subsequently required mechanical ventilation. His X-ray showed pulmonary edema and both nitroprusside and nitroglycerine were added to the milrinone. Sepsis, pulmonary hypertension, renal failure and pneumonia complicated his hospital course. He was discharged, milrinone dependant on day 47.

61) Subject # 675-402 (NAT adjustable dose, catheterized) (69 y/o F, Class IV). She was treated for 26 hours with study drug that was stopped due to inadequate clinical response. She was discharged on day 5 but readmitted the next day with symptoms of dyspnea. She also had renal insufficiency and diarrhea. She was treated with inotropes and discharged on day 14.

62) Subject # 678-401 (NAT, adjustable dose) (60 y/o M NYHA III). He was treated for 2 days and discontinued due to clinical improvement. He was discharged on day 3 but readmitted on day 28 for a syncopal episode attributed to phenrgan and dehydration. Diuretics and Vasotec were adjusted and carvedilol was administered. He was discharged on day 31.

Subjects whose Dose was interrupted or decreased:

There were three subjects who discontinued during the initial 3-hour infusion

1) Subject #357-502 (Natrecor fixed dose, not catheterized) This patient's course is described under deaths.

2) Subject #369-518 (NAT, fixed dose, not catheterized) (59 y/o M, NYHA III). He was initially enrolled for dobutamine therapy and was started on therapy. After approximately 1.5 hours after the start of therapy, the subject had a severe drop in blood pressures from approximately 95/59 to 60/27 mm Hg. The study drug was discontinued. The systolic blood pressure remained below 90 mm Hg for 2 hours.

3) Subject # 543-405 (PBO/NTG, catheterized) (64 y/o F, NYHA II). This subject was started on study drug despite not meeting prespecified criteria for wedge pressures. There were apparently no adverse events but the study drug was discontinued after approximately 4.5 hours. The wedge pressure at the time was 12 mm Hg. Wedge pressures were measured through 15 hours. Dyspnea assessed during the 24-hour observation period.

Adverse Events Labeled as Severe: There were a total of 152 subjects that had one or more adverse events listed as "severe" in intensity. The numbers of subjects with events listed as severe in intensity are shown in Table41. This reviewer attempted to enumerate those subjects with CHF or renal events of "severe" intensity. The inclusion by this reviewer was somewhat subjective. For example, subjects described as having respiratory failure or respiratory arrest in were treated as having worsening CHF. Subjects were counted under renal events who had events described as hyperkalemia, azotemia or uremia.

Table 41. Summary of events listed as "severe" in intensity

	Catheterized					Not Catheterized				Totals	
	NTG	FIX NAT	ADJ NAT	PBO: NTG	PBO: NAT	NTG	NAT	PBO: NTG	PBO: NAT	All NTG	All Fixed NAT
N=	60	62	62	32	30	83	80	41	39	216	211
Pts with events as severe	24 (39%)	20 (32%)	19 (30%)	10 (31%)	10 (32%)	22 (27%)	23 (28%)	11 (27%)	13 (32%)	69 (32%)	64 (30%)
CHF-related events	13 (21%)	11 (17%)	13 (21%)	3 (9%)	4 (13%)	12 (14%)	14 (17%)	8 (20%)	5 (13%)	36 (17%)	33 (16%)
Renal events	5 (8%)	5 (8%)	4 (6%)	0 (0%)	0 (0%)	2 (2%)	7 (8%)	2 (7%)	2 (5%)	9 (4%)	14 (7%)

Major Events monitored by the DSMC through day 30: Table 42 contains the number of major adverse events that were monitored by the DSMC for the first 30 days following the index infusion and include cerebrovascular accidents, myocardial infarctions, new onset dialysis and death. Deaths are summarized and tabulated above.

Table 42 Major events monitored by the DSMC through day 30

	NTG (n=216)	NAT fixed dose (N=211)	All NAT (n=273)
Cerebrovascular accident	1 (<1%)	0	0
Myocardial infarction	3 (1%)	1 (<1%)	2 (1%)
New onset dialysis	5 (2%)	7 (3%)	9 (3%)
Deaths	11 (5%)	15 (7%)	22 (8%)

Overall Adverse Events:

Adverse events during the placebo-controlled period: The adverse events during the 3-hour placebo-controlled phase are shown in Table 43. There was an increase in events in the NTG group, with nearly all the differences due to headache. Relative to placebo, headache was numerically increased in the Natrecor-treated patients.

Table 43 Events occurring in > 2 subjects in any one group 3-hour placebo controlled phase.

	NTG (N=143)	NAT (N=204)	PBO (N=142)
Any Adverse Event	39 (27%)	36 (18%)	20 (14%)
Headache	17 (12%)	11 (5%)	3 (2%)
Pain	2 (1%)	2 (1%)	2 (1%)
Hypotension	6 (4%)	5 (2%)	0
Symptomatic hypotension	2 (1%)	1 (<1%)	0
Abdominal pain	4 (3%)	0	0
Catheter pain	2 (1%)	0	0
Injection site reaction	0	2 (1%)	0
Neck pain	0	0	2 (1%)
Ventricular tachycardia	2 (1%)	2 (1%)	0
NSVT	2 (1%)	2 (1%)	0
Anxiety	0	3 (1%)	3 (2%)
Nervousness	2 (1%)	2 (1%)	0
Angina pectoris	0	2 (1%)	1 (1%)
Hyperkinesia	0	2 (1%)	0
Nausea	2 (1%)	1 (< 1 %)	1 (1%)

Adverse events through 24-hours: A tabulation of adverse events during the first 24-hours of infusion (Table 44) shows an increase in adverse events among the NTG treated subjects (68% to ~50%). The difference between the NTG and NAT groups is largely accounted for by the increased incidence of headache and nausea in the nitroglycerin group relative to the two cohorts of Natrecor

treated subjects. The event rate in the Natrecor adjustable dose group can be determined by subtracting the Nat fixed dose event rate from the all Natrecor event rate and dividing by the number of subjects treated with Natrecor, adjustable dose (N=62). There does not appear to be any large increase in adverse events in the Natrecor, adjustable dose cohort. Hypotension (both asymptomatic and symptomatic) differs minimally in comparing the three cohorts.

Table 44 Adverse events during first 24 hours > 1 ADR in any group

Adverse events	NTG (N=216)	NAT, fixed dose (N=211)	All NAT (N=273)
Any Adverse events	146 (68%)	105 (50%)	140 (51%)
Body as a whole			
Headache	44 (20%)	19 (9%)	21 (8%)
Pain	11(5%)	8 (4%)	11 (4%)
Back Pain	7 (3%)	9 (4%)	10 (4%)
Abdominal pain	11 (5%)	2 (1%)	4 (1%)
Catheter pain	11 (5%)	3 (1%)	4 (1%)
Asthenia	4 (2%)	1 (< 1%)	1 (< 1%)
Fever	5 (2%)	2 (1%)	3 (1%)
Injection site reaction	4 (2%)	3 (1%)	4 (1%)
Digestive			
Nausea	13 (6%)	7 (3%)	10 (4%)
Vomiting	4 (2%)	3 (1%)	4 (1%)
Constipation	4 (2%)	3 (1%)	3(1%)
Diarrhea	4 (2%)	2 (1%)	2 (1%)
Cardiovascular			
Asymptomatic hypotension	17 (8%)	17 (8%)	23 (8%)
Symptomatic hypotension	10 (5%)	10 (5%)	12 (4%)
Non-sustained VT	11 (5%)	6 (3%)	9 (3%)
Ventricular extrasystoles	2 (1%)	4 (2%)	7 (3 %)
Atrial fibrillation	1 (< 1%)	4 (2%)	4 (1%)
Angina pectoris	5 (2%)	4 (2%)	5 (2%)
Nervous			
Insomnia	9 (4%)	3 (1%)	6 (2%)
Anxiety	6 (3%)	6 (3%)	8 (3%)
Dizziness	4 (2%)	7 (3%)	7 (3%)
Confusion	5 (2%)	1 (< 1%)	2 (1%)
Metabolic and nutritional disorders			
Hypokalemia	1 (< 1%)	4 (2%)	6 (2%)
Hypoglycemia	4 (2%)	1 (<1%)	2(1%)
Respiratory			
Cough Increased	4 (2%)	1 (<1%)	1(< 1%)

Adverse events through day 14: Adverse events that occurred during the first fourteen days of the study, independent of the continuation of infusion, are shown in Table 45. Headache is still more common in the nitroglycerin cohort. “Kidney function abnormal” was more frequent in the “All Natrecor” cohort. The difference can be attributed to the 11% incidence (7 event in 62 subjects) of abnormal function in the adjustable Natrecor cohort.

Table 45 Adverse events through 14 days > 3 % in any group, not corrected for duration of hospitalization or treatment.

	NTG (N=216)	Natrecor , fixed dose (N=211)	All Natrecor (N=273)
Any Event	185 (86%)	170 (81%)	219 (80%)
Body as a whole			
Headache	56 (26%)	46 (22%)	54 (20%)
Pain	32 (15%)	29 (14%)	37 (14%)
Back pain	15 (7%)	18 (9%)	23 (8%)
Abdominal pain	22 (10%)	11 (5%)	15 (5%)
Fever	11 (5%)	13 (6%)	15 (5%)
Asthenia	14 (6%)	10 (5%)	10 (4%)
Catheter pain	14 (6%)	6 (3%)	10 (4%)
Chest pain	11 (5%)	6 (3%)	11 (4%)
Injection site pain	8 (4%)	5 (2%)	8 (2%)
Cardiovascular			
Hypotension Total	51 (24%)	51 (24%)	63 (23%)
Hypotension-symptomatic	18 (8%)	24 (11%)	28 (10%)
Hypotension asymptomatic	37 (17%)	33 (16%)	42 (15%)
VT-sustained	4 (2%)	4 (2%)	5 (2%)
VT-non-sustained	28 (13%)	26 (12%)	32 (12%)
CHF	19 (9%)	16 (8%)	22 (8%)
Angina pectoris	16 (7%)	17 (8%)	20 (7%)
Ventricular extrasystoles	4 (2%)	8 (4%)	12 (4%)
Atrial fibrillation	3 (1%)	9 (4%)	9 (3%)
Bradycardia	3 (1%)	8 (4%)	9 (3%)
SVT	0	5 (2%)	6 (2%)
Heart arrest	0	5 (2%)	5 (2%)
Nervous			
Insomnia	27 (13%)	23 (11%)	31 (11%)
Dizziness	20 (9%)	21 (10%)	25 (9%)
Anxiety	12 (6%)	15 (7%)	17 (6%)
Confusion	14 (6%)	9 (4%)	12 (4%)
Nervousness	6 (3%)	7 (3%)	8 (3%)
Agitation	7 (3%)	2 (1%)	2 (1%)
Digestive			
Nausea	26 (12%)	33 (16%)	38 (14%)
Constipation	15 (7%)	15 (7%)	18 (7%)
Vomiting	13 (6%)	15 (7%)	16 (6%)
Diarrhea	9 (4%)	12 (6%)	15 (5%)
Dyspepsia	6 (3%)	8 (4%)	10 (4%)
Respiratory			
Dyspnea	12 (6%)	14 (7%)	15 (5%)
Cough increased	12 (6%)	6 (3%)	8 (3%)
Apnea	6 (3%)	4 (2%)	5 (2%)
Urogenital			
Kidney function abnormal	8 (4%)	11 (5%)	18 (7%)
Urinary tract infection	7 (3%)	8 (4%)	9 (3%)
Creatinine increased	7 (3%)	4 (2%)	5 (2%)
Metabolic and nutritional			
Hypoglycemia	9 (4%)	7 (3%)	9 (3%)
Hyperkalemia	6 (3%)	7 (3%)	8 (3%)
Hypokalemia	2 (1%)	7 (3%)	9 (3%)
BUN Increased	6 (3%)	2 (1%)	2 (1%)
Musculoskeletal			
Arthralgia	5 (2%)	8 (4%)	12 (4%)
Hemic and lymphatic			
Anemia	6 (3%)	6 (3%)	10 (4%)

[Comment: the duration of hospitalization and therefore the duration of observation among the different cohorts confound the apparent event rate listed in Table 45. Since the duration of hospitalization for Natrecor subjects is slightly longer than that for NTG subjects, any increase in event rate over the 14-day period may reflect a greater observation period than a true increase in event rate.]

Laboratory: Chemistry: No routine chemistry profiles were performed. Only serum creatinine measurements were performed at baseline, end of the 24-hour infusion, daily for two days post infusion, once somewhere between day 14-19 and once between day 30-35.

Renal function: This study did not have an enrollment requirement that excluded subjects with elevated baseline creatinine measurements. Those enrolled had large variability in their baseline renal function. Some subjects who enrolled were described as having chronic renal failure. The mean and median changes in creatinine in this study are shown in Table 46. There were small changes in serum creatinine over the course of the assessments. These differences were not statistically (nominally) different.

Table 46 Creatinine changes during and after the infusion.

	NTG (N=216)	NAT fixed dose (N=211)	Nat Adjust Dose (N=62)
Baseline			
Mean ± SD	1.6± 1.0	1.6 ± 1.1	1.7 ± 0.79
Median (25-75%)	1.3 (1.0-1.9)	1.4 (1.0-1.8)	1.5 (1.1-2.0)
N/ (missing values)	212 (4)	209 (2)	60 (2)
> 2.0 mg/dL	44 (21%)	45 (22%)	15 (25%
Day 2 (>0 -48 Hrs)			
Mean ± SD	1.5 ± 0.9	1.7 ± 1.2	1.6 ± 0.8
Median (25-75%)	1.3 (1.0-1.8)	1.4 (1.0-1.8)	1.4 (1.0-1.8)
N/ (missing values)	213 (3)	209 (2)	62 (0)
Day 5 (> 48 Hrs-7 days)			
Mean ± SD	1.6± 0.76	1.7± 1.2	1.7 ± 1.1
Median (25-75%)	1.4 (1.1-1.9)	1.5 (1.0-1.9)	1.4 (1.1-2.0)
N/ (missing values)	168 (48)	169 (42)	49 (13)
Day 14 (day 8-19)			
Mean ± SD	1.7± 1.1	1.9 ± 1.5	1.7 ± 0.7
Median (25-75%)	1.4 (1.1-2.0)	1.4 (1.1-2.1)	1.5 (1.2-1.9)
N/ (missing values)	163 (53)	166 (45)	44 (18)
Day 30 (Day 20-40)			
Mean ± SD	1.7 ± 1.1	1.8 ± 1.4	1.7 ± 1.2
Median (25-75%)	1.3 (1.1-1.8)	1.4 (1.1-2.0)	1.4 (1.2-1.9)
N/ (missing values)	173 (43)	167 (44)	51 (11)

Dialysis: The number of subjects who were newly dialyzed is listed in Table 42 above.

Extremes in creatinine:

Table 47 lists those subjects whose creatinine rose by greater than 0.5 mg/dl. The table includes the first value above this cut-off and the day post-infusion that it occurred, the worst such value (and the day it occurred) and the last available value for the subject if different than the worst value (and day). Those subjects **in bold** have their last creatinine above the 0.05 mg/dl increase above baseline at their last creatinine measurements.

Table 47 subjects whose creatinine increased greater than 0.5 from baseline. Subjects in bold are still abnormal (> 0.5 mg/dl increase above baseline) at the end of the observation period. Within each treatment, subjects are listed according to baseline value.
ANAT= Adjustable dose Natrecor, catheterized; FNAT-fixed dose Natrecor, NTG= nitroglycerin, PLA: NTG-Placebo-nitroglycerin; PLA:NAT-placebo-then Natrecor. NC=Not Catheterized, C=Catheterized. √=Abnormal within first week

	pt #	Tx	Baseline	First abnormal (day)	Worse abnormal (time)	last (time)
1	642-405	ANAT	0.6	1.4 (4) √	1.4 (4)	0.9 (30)
2	**667-408**	**ANAT**	**0.8**	**1.6 (15)**	**1.6 (15)**	**1.4 (32)**
3	**687-413**	**ANAT**	**1.2**	**1.8 (26)**	**1.8 (26)**	
4	572-402	ANAT	1.2	2.2 (3) √	2.2 (3)	1.1 (31)
5	554-412	ANAT	1.5	2.4 (3) √	2.4 (3)	1.5 (18)
6	667-414	ANAT	1.5	2.7 (15)	2.7 (15)	1.7 (32)
7	**579-401**	**ANAT**	**1.5**	**2.2 (18)**	**2.2 (18)**	**2.1 (35)**
8	**620-401**	**ANAT**	**1.5**	**3.0 (16)**	**3.0 (16)**	**2.2 (35)**
9	**642-406**	**ANAT**	**1.5**	**2.5 (15)**	**2.5 (15)**	
10	**369-419**	**ANAT**	**1.9**	**2.5 (5) √**	**2.7 (19)**	**2.6 (28)**
11	**675-402**	**ANAT**	**1.9**	**2.7 (17)**	**4.5 (33)**	
12	**688-401**	**ANAT**	**2.2**	**3.1 (3) √**	**6.0 (6)**	
13	**369-409**	**ANAT**	**2.7**	**3.8 (16)**	**3.8 (16)**	**3.6 (33)**
14	554-409	ANAT	3.6	5.5 (6) √	7.4 (9)	2.5 (25)
15	**538-403**	**ANAT**	**3.6**	**8.9 (33)**	**8.9 (33)**	
16	**667-407**	**FNAT,C**	**0.8**	**1.4 (3) √**	**2.0 (4)**	**1.6 (32)**
17	554-404	FNAT,C	0.9	2.1 (4) √	2.6 (5)	1.2 (16)
18	585-401	FNAT,C	1.0	1.6 (17)	1.6 (17)	0.9 (30)
19	636-404	FNAT,C	1.2	2.1 (19)	2.1 (19)	1.6 (29)
20	**605-401**	**FNAT,C**	**1.2**	**2.0 (28)**	**2.0 (28)**	
21	667-411	FNAT,C	1.4	2.2 (15)	2.2 (15)	1.8 (31)
22	**667-401**	**FNAT,C**	**1.4**	**2.0 (21)**	**2.0 (31)**	
23	**667-415**	**FNAT,C**	**1.5**	**6.7 (16)**	**6.7 (16)**	**2.5 (30)**
24	540-408	FNAT,C	1.6	2.2 (16)	2.2 (16)	2.0 (30)
25	**540-403**	**FNAT,C**	**1.6**	**2.7 (4) √**	**3.1(5)**	**2.4 (14)**
26	687-422	FNAT, C	1.8	2.6 (22)	2.6(22)	2.2 (29)
27	642-403	FNAT,C	1.9	3.4 (15)	3.4 (15)	1.4 (32)
28	580-401	FNAT,C	2	2.6 (4) √	2.8 (13)	2.1 (35)
29	**675-401**	**FNAT,C**	**2.1**	**5.0 (37)**	**5.0 (37)**	
30	668-401	FNAT,C	2.2	2.8 (15)	2.8 (15)	2.1 (30)
31	551-401	FNAT,C	2.3	3.8 (2) √	5.3 (4)	1.6 (30)
32	580-407	FNAT,C	2.6	3.8 (20)	3.8 (20)	2.6 (51)
33	**572-410**	**FNAT,C**	**11.1**	**11.7 (29) √**	**11.7 (29)**	**11.7 (29)**
34	681-502	FNAT,NC	0.8	1.4 (14)	1.4 (14)	0.9 (28)
35	**642-503**	**FNAT,NC**	**0.8**	**1.7 (14)**	**1.7 (14)**	**1.4 (31)**
36	**636-502**	**FNAT,NC**	**1**	**2.1 (161)**	**3.8 (163)**	**3.0 (164)**
37	**554-522**	**FNAT,NC**	**1.1**	**1.8 (3) √**	**1.8 (3)**	**1.8 (30)**
38	618-502	FNAT,NC	1.3	2.3 (3) √	2.3 (3)	1.4 (14)
39	502-501	FNAT,NC	1.4	2.1 (3) √	2.1 (3)	1.6 (30)
40	679-502	FNAT,NC	1.4	2.0 (14)	2.0 (18)	1.6 (39)
41	**369-519**	**FNAT,NC**	**1.5**	**2.2 (30)**	**2.2 (30)**	
42	560-501	FNAT,NC	1.6	3.1 (14)	3.1 (14)	1.4 (33)
43	382-504	FNAT,NC	1.6	2.4 (15)	2.4 (15)	1.5 (30)
44	**369-514**	**FNAT,NC**	**1.8**	**4.5 (14)**	**4.5 (14)**	**4.0 (30)**
45	**369-503**	**FNAT,NC**	**1.8**	**3.6 (15)**	**3.6 (15)**	
46	**678-513**	**FNAT,NC**	**1.9**	**3.7 (15)**	**3.7 (15)**	**2.6 (29)**
47	**561-503**	**FNAT,NC**	**2.2**	**3.0 (15)**	**3.0 (15)**	**2.9 (35)**

48	**627-506**	**FNAT,NC**	**2.2**	**3.4 (5) √**	**3.6 (6)**	
49	**627-505**	**FNAT,NC**	**2.7**	**3.6 (6) √**	**3.6 (6)**	**3.6 (14)**
50	**605-508**	**FNAT,NC**	**2.7**	**3.7 (16)**	**3.7 (16)**	
51	**572-502**	**FNAT,NC**	**2.9**	**5.2 (14)**	**6.0 (30)**	
52	**554-545**	**FNAT,NC**	**3.4**	**4.5 (3) √**	**7.9 (16)**	**6.7 (33)**
53	**551-402**	**PLA:NAT,C**	**1.1**	**1.7 (33)**	**1.7 (33)**	
54	**369-411**	**PLA:NAT,C**	**1.2**	**2.8 (38)**	**2.8 (38)**	
55	**663-407**	**PLA:NAT,C**	**1.4**	**2.4 (33)**	**2.4 (33)**	
56	666-408	PLA:NAT,C	1.5	2.8 (17)	2.8 (17)	1.1 (36)
57	367-403	PLA:NAT,C	1.6	2.5 (16)	2.5 (16)	1.9 (28)
58	671-401	PLA:NAT,C	1.7	2.4 (18)	2.4 (18)	1.6 (26)
59	**580-403**	**PLA:NAT,C**	**1.9**	**2.9 (33)**	**2.9 (33)**	
60	551-404	PLA:NAT,C	2.3	3.1 (4) √	3.1 (4)	1.3 (18)
61	687-420	PLA:NAT,C	2.4	3.7 (7)	3.7 (7)	2.4 (36)
62	**687-415**	**PLA:NAT,C**	**3.6**	**4.7 (36)**	**4.7 (36)**	
63	**681-503**	**PLA:NAT,NC**	**1**	**1.6 (29)**	**1.6 (29)**	
64	502-505	PLA:NAT,NC	1.1	4.2 (3) √	4.3 (3)	1.0 (38)
65	679-501	PLA:NAT,NC	1.2	2.0 (18)	2.0 (18)	1.1 (36)
66	605-505	PLA:NAT,NC	1.3	2.4 (3) √	2.5 (3)	1.1 (29)
67	666-510	PLA:NAT,NC	1.3	3.1 (16)	3.1 (16)	1.3 (32)
68	369-513	PLA:NAT,NC	1.8	2.5 (3) √	2.5 (3)	2.2 (33)
69	**636-504**	**PLA:NAT,NC**	**1.8**	**3.0 (14)**	**3.0 (14)**	**2.5 (31)**
70	**382-501**	**PLA:NAT,NC**	**2**	**2.9 (30)**	**2.9 (30)**	
71	554-515	PLA:NAT,NC	2.9	3.6 (3) √	3.6 (3)	2.3 (17)
72	**627-502**	**PLA:NAT,NC**	**3.9**	**4.5 (2) √**	**9.0 (15)**	**6.7 (32)**
73	**554-523**	**PLA:NAT,NC**	**4.7**	**6.9 (7)**	**6.9 (7)**	
74	**678-502**	**PLA:NAT,NC**	**5.3**	**6.4 (32)**	**6.4 (32)**	
75	**369-512**	**PLA:NAT,NC**	**6.5**	**7.5 (30)**	**7.5 (30)**	
76	554-426	NTG,C	0.8	1.4 (2) √	1.4 (2)	1.0 (27)
77	**667-404**	**NTG,C**	**1**	**1.7 (4) √**	**2.0 (17)**	**1.8 (32)**
78	**580-402**	**NTG,C**	**1.1**	**1.9 (15)**	**1.9 (15)**	**1.9 (32)**
79	687-410	NTG,C	1.3	1.9 (2)	1.9 (2)	1.6 (16)
80	667-409	NTG,C	1.9	2.6 (16)	2.6 (16)	1.3 (30)
81	**687-417**	**NTG,C**	**1.9**	**2.6 (32)**	**2.6 (32)**	
82	711-403	NTG,C	1.9	2.7 (4) √	2.7 (4)	1.6 (33)
83	554-417	NTG,C	2	2.7 (5) √	2.7 (5)	2.3 (39)
84	**543-404**	**NTG,C**	**2.1**	**3. (15)**	**5.3 (31)**	
85	**627-402**	**NTG,C**	**2.5**	**6.1 (18)**	**6.1 (18)**	**5.5 (31)**
86	538-406	NTG,C	3.3	4.9 (14)	4.9 (14)	1.6 (32)
87	**382-405**	**NTG,C**	**3.4**	**4.1 (15)**	**4.1 (15)**	
88	**502-403**	**NTG,C**	**4**	**5.1 (16)**	**5.9 (33)**	
89	554-528	NTG,C	0.9	1.5 (2) √	1.5 (2)	0.9 (31)
90	**681-504**	**NTG,NC**	**1.1**	**1.7 (14)**	**1.7 (14)**	
91	360-503	NTG,NC	1.2	1.9 (2) √	2.0 (3)	1.6 (36)
92	**605-502**	**NTG,NC**	**1.3**	**2.3 (17)**	**2.4 (30)**	
93	554-407	NTG,NC	1.5	2.4 (17)	2.4 (17)	1.8 (33)
94	**516-501**	**NTG,NC**	**1.5**	**2.1 (30)**	**2.1 (30)**	
95	**357-503**	**NTG,NC**	**1.7**	**2.8 (15)**	**2.8(15)**	
96	**627-507**	**NTG,NC**	**2.1**	**2.7 (3) √**	**4.6 (16)**	**4.6 (1)**
97	516-502	NTG,NC	2.2	3.5 (14)	3.5 (14)	2.4 (30)
98	**524-503**	**NTG,NC**	**2.4**	**4.2 (15)**	**4.2 (15)**	**3.3 (30)**

99	**636-505**	**NTG,NC**	**2.5**	**3.5 (19)**	**3.5 (19)**	
100	**580-501**	**NTG,NC**	**3.1**	**5.7 (32)**	**5.7 (32)**	
101	**678-508**	**NTG.NC**	**4.2**	**5.5 (30)**	**5.5 (30)**	
102	687-421	PLA:NTG, C	1.9	2.7 (17)	2.7 (17)	1.6 (31)
103	666-402	PLA:NTG,C	1.1	2.7 (19)	2.7 (19)	1.0 (32)
104	580-410	PLA:NTG,C	1.1	1.7 (13)	1.7 (13)	1.1 (31)
105	**369-407**	**PLA:NTG,C**	**1.2**	**2.2 (16)**	**5.5 (27)**	
106	663-404	PLA:NTG,C	1.3	2.0 (16)	2.0 (16)	1.5 (36)
107	687-405	PLA:NTG,C	1.5	2.3 (4) √	2.3 (4)	1.4 (33)
108	687-406	PLA:NTG,C	1.7	2.3 (7)	2.3 (7)	1.7 (11)
109	**618-401**	**PLA:NTG,C**	**1.9**	**3.2 (18)**	**3.2 (18)**	
110	687-424	PLA:NTG,C	0.8	1.6 (3) √	1.6 (3)	1.0 (38)
111	360-502	PLA:NTG,NC	0.5	1.3 (18)	1.3 (18)	0.9 (33)
112	666-508	PLA:NTG,NC	0.8	2.5 (3) √	2.5 (3)	1.2 (26)
113	663-510	PLA:NTG,NC	1.3	2.7 (3) √	2.7 (3)	1.5 (34)
114	642-502	PLA:NTG,NC	1.5	2.6 (14)	2.6 (14)	1.6 (31)
115	357-406	PLA:NTG,NC	1.5	2.1 (16)	2.1 (16)	1.9 (31)
116	**369-501**	**PLA:NTG,NC**	**1.5**	**2.3 (14)**	**2.8 (31)**	
117	**554-512**	**PLA:NTG,NC**	**2.2**	**2.8 (31)**	**2.8 (31)**	
118	**666-505**	**PLA:NTG,NC**	**2.2**	**2.9 (3) √**	**3.2 (4)**	
119	502-506	PLA:NTG,NC	3.2	3.9 (14)	3.9 (14)	3.7 (35)
120	554-514	PLA:NTG.NC	1.2	2.6 (4) √	2.6 (4)	1.2 (33)

Table 48 Summary of renal effects from Table 47

	Catheterized					Not Catheterized				All	
	NTG	FIX: NAT	ADJ NAT	PBO: NTG	PBO: NAT	NTG	NAT	PBO: NTG	PBO: NAT	NTG	NAT, fixed
N=	62	63	63	32	31	83	82	41	41	216	211
# with Cr increase of > 0.5 mg/dl (%)	14 (23%)	18 (29%)	15 (24%)	9 (28%)	10 (32%)	12 (14%)	19 (23%)	10 (24%)	12 (24%)	45 (21%)	59 (28%)
# abnormal within first week	5 (8%)	6 (10%)	6 (10%)	2 (6%)	1 (3%)	2 (2%)	6 (7%)	4 (10%)	5 (13%)	13 (6%)	18 (9%)
# with abnormal at last value	7 (11%)	7 (11%)	10 (14%)	2 (7%)	5 (16%)	9 (11%)	13 (16%)	3 (8%)	7 (17%)	21 (10%)	30 (14%)

Hematology: Not routinely captured on the CRFs.

Urinalysis: Urinalysis was not routinely captured on the CRFs.

ECG: ECGs were not routinely collected.

Vital Signs: The vital signs for the first three hours are shown in figures 10 and 11. There were no differences between nitroglycerine (NTG) and Natrecor (NAT). Both active treatments decreased systolic blood pressure relative to placebo at 1/2, 2 and 3 hours. NTG also significantly lowered SBP at 1 hour. With respect to diastolic blood pressures, both treatments were significantly different than placebo at ½, hour only. Heart rates did not differ (Figure 12) among treatments.

Figure 10

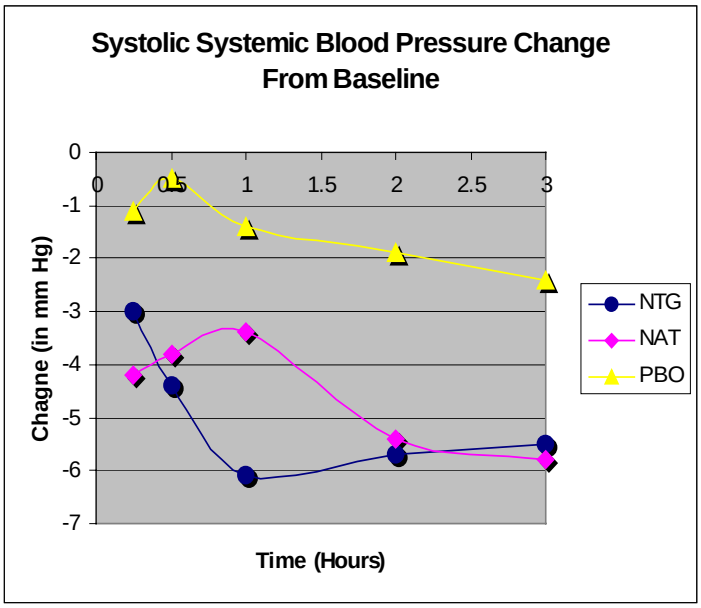


Figure 11

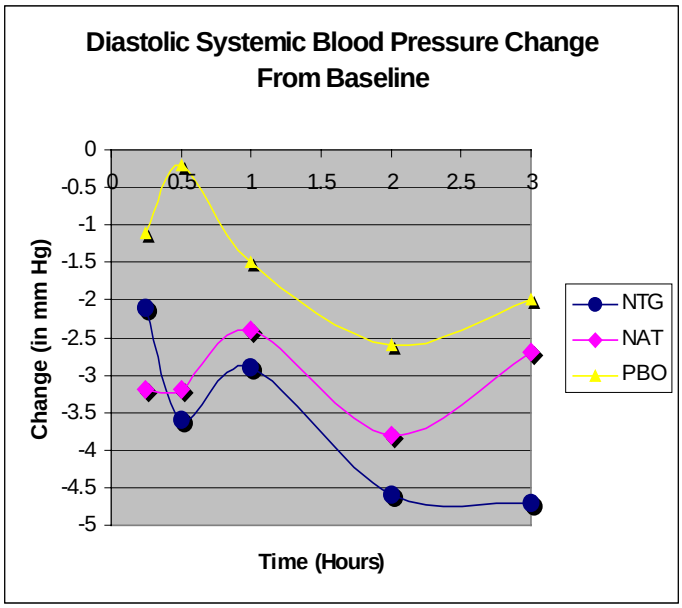
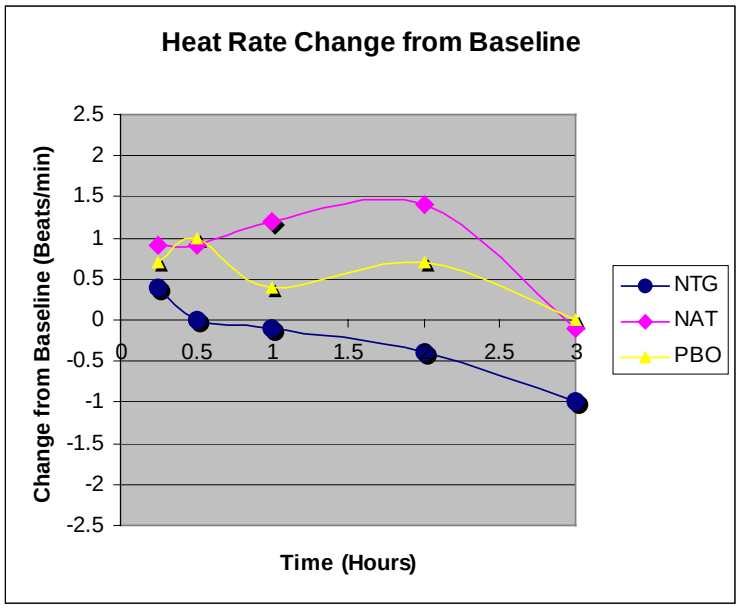


Figure 12



Vital signs after 3 hours are shown in Figure 13-15. Both the NAT fixed and NTG all include those placebo crossover subjects. The NAT fixed (ALL) excludes those in the NAT adjustable dose group. The other three groups graphed reflect those catheterized. The change reflects baseline changes. The three-hour time point for the cohorts were not available so that equivalence when the placebo subjects were reallocated is not shown. Systolic blood pressure was decreased at the 9-hour time point for the Natrecor, adjustable dose. Diastolic blood pressures show no difference between any Natrecor infusion and nitroglycerin. Heart rates show no reflexive tachycardia in response to the blood pressure decreases.

Figure 13

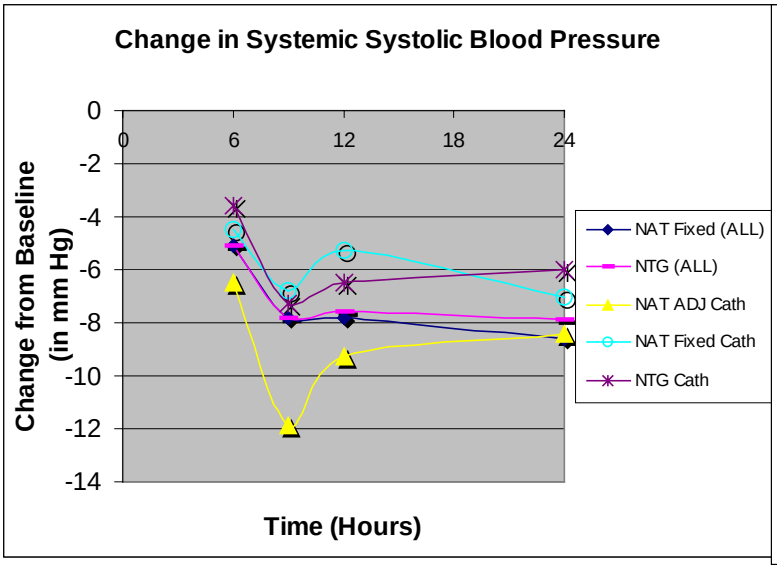


Figure 14

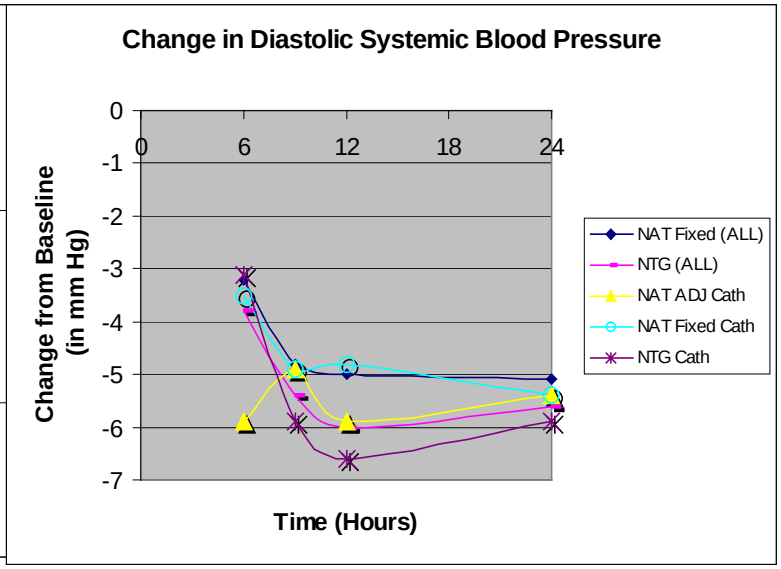
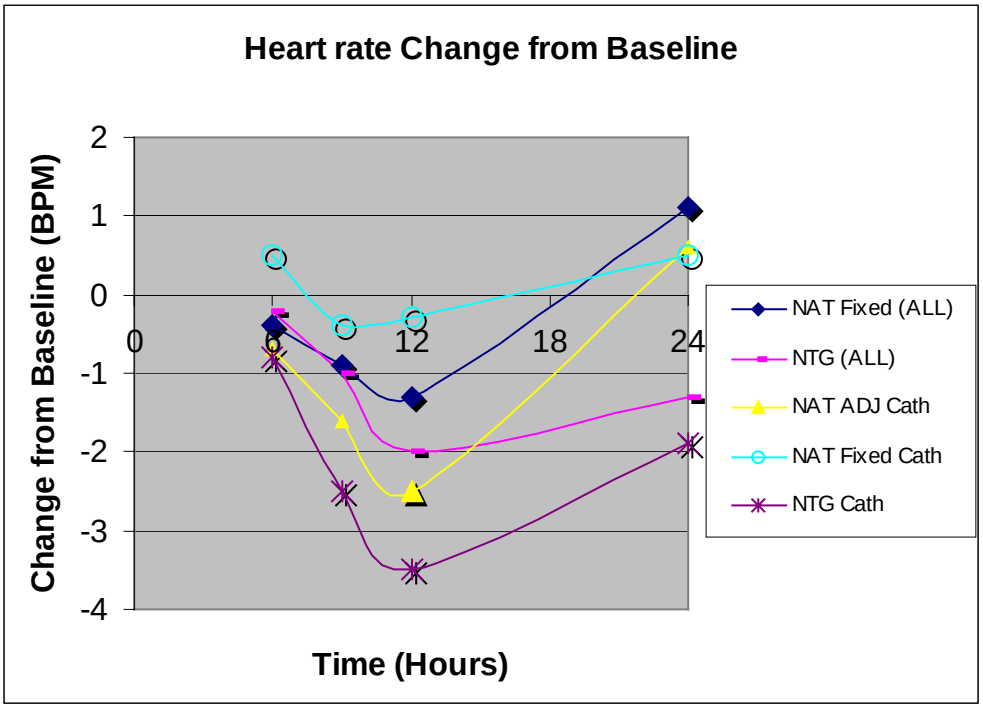


Figure 15



Episodes of Hypotension: This data is derived from Table 109.1 of the sponsor. There were several representations of the data. Table 48 reflects hypotensive events during the entire infusion period (which for many subjects was longer than 24 hours). Other tabular listings that describe the events during the first 24 hours do not significantly differ from this table. The number of episodes was approximately the same for nitroglycerin or Natrecor. The duration of the hypotensive episodes for the Natrecor treated subjects was longer.

Table 48 Description of hypotensive episodes -study 704.339.

	NTG (N=216)	Natrecor, fixed dose (N=211)	All Natrecor (N=273)	Natrecor Adjust (N=62)
Number With at ≥ 1 episode	12 (6%)	13 (6%)	15 (5%)	2 (3%)
Number of episodes	13	16	18	2
Time of onset (episode)				
< 1Hour	0	0	0	0
>1-3 Hour	1 (8%)	0	0	0
>3-6 Hour	3 (23%)	4 (25%)	4 (22%)	0
>6-24 Hour	7 (54%)	8 (50%)	10 (56%)	2 (100%)
>24 –48 Hour	2 (15%)	2 (13%)	2 (11%)	0
> 48 Hour	0	2 (13%)	2 (11%)	0
Duration of episode				
≤ 30 minutes	7 (54%)	0	0	0
31-60 minutes	2 (15%)	4 (25%)	4 (22%)	0
61-120 minutes	4 (31%)	5 (31%)	5 (28%)	0
121-180 minutes	0	4 (25%)	5 (28%)	1 (50%)
3- 7 hours	0	3 (19%)	4 (22%)	1 (50%)
> 7 hours	0	0	0	0
Severity of episode				
Mild	7 (54%)	6 (38%)	6 (33%)	0
Moderate	5 (38%)	8 (50%)	10 (56%)	2 (100%)
Severe	1 (8%)	2 (13%)	2 (11%)	0
Effect of Study Drug				
None/increased	3 (23%)	1 (6%)	1 (6%)	0
Decreased/ Interrupted	5 (38%)	6 (38%)	8 (44%)	2 (100%)
Discontinued	5 (38%)	9 (56%)	9 (50%)	0
All predominant /reported Symptoms				
Lightheadedness	4 / 7	7/11	9/13	2/2
Dizziness	4/10	7/12	7/14	0/2
Feeling Faint	1/ 2	0/3	0/3	0/0
Blurred vision	0/1	0/1	0/1	0/0
other	4/9	2/5	2/6	0/1
Additional action taken				
None	5	10	12	2
Volume challenge	4	2	2	0
Trendelenburg position	3	2	2	0
Dopamine initiated	1	0	0	0
Dopamine increased	0	0	0	0
Inotrope/pressor added	0	1	1	0
Inotrope/ pressor added	0	1	1	0
Other meds added/ increased	0	0	0	0
Other meds decreased/discontinued	0	0	0	0
Hospitalized	0	0	0	0
Other	2	1	1	0
Med decreased	1	0	0	0

With respect to the impact of catheterization, there were more hypotensive events among the NTG subjects who were catheterized versus those who were not catheterized (9% versus 3 %). In all likelihood this difference reflects the higher dose of NTG among those catheterized. Among the Natrecor subjects, there were a greater fraction of those not catheterized who had events when compared to those catheterized (4% versus 8%).

Table 49 Hypotension among those catheterized and not catheterized

	NTG subjects		NAT subjects	
	Catheterized (N=92)	Not catheterized (N=124)	Catheterized Fixed + Adjustable (N=154)	Not catheterized (N=119)
Number With at ≥ 1 episode	8	4	6	9
Number of episodes	8	5	6	12
Time of onset (episode)				
< 1Hour	0	0	0	0
>1-3 Hour	1 (13%)	0	0	0
>3-6 Hour	1 (13%)	2(40%)	0	4 (33%)
>6-24 Hour	5 (63%)	2 (40%)	5 (83%)	5(42%)
>24 –48 Hour	1 (13%)	1 (20%)	0	2 (17%)
> 48 Hour	0	0	1 (17%)	1 (8%)
Duration of episode				
≤ 30 minutes	5 (63%)	2 (40%)	0	0
31-60 minutes	1 (13%)	1 (20%)	2 (33%)	2 (17%)
61-120 minutes	2 (25%)	2 (40%)	2 (33%)	3 (25%)
121-180 minutes	0	0	1 (17%)	4 (33%)
3- 7 hours	0	0	1 (17%)	3 (25%)
> 7 hours	0	0	0	0
Severity of episode				
Mild	6 (75%)	1 (20%)	3 (50%)	3 (25%)
Moderate	1 (13%)	4 (80%)	2 (33%)	8 (67%)
Severe	1 (13%)	0	1 (17%)	1 (8%)
Effect of Study Drug				
None/increased	2 (25%)	1(20%)	0	1 (8%)
Decreased/ Interrupted	4 (50%)	1 (20%)	2 (33%)	6 (50%)
Discontinued	2 (25%)	3 (60%)	4 (67%)	5 (42%)
All reported /predominant Symptoms				
Lightheadedness	3/ 0	4/4	6/4	7/5
Dizziness	6/4	4/0	4/2	10/5
Feeling Faint	1/ 1	1/0	0/0	3/0
Blurred vision	1/1	0/0	0/0	1/0
other	6/3	3/1	2/0	4/2

Bradycardia: Bradycardia was an infrequent adverse event reported either through 24 hours or 14 days of the study. As of 48-hours of the infusion there were 3 episodes of bradycardia (1%) in the Natrecor fixed dose group and 1 (< 1%) of those treated with nitroglycerin. During the 14-day observation period 4% of those treated with Natrecor and 1% of those with nitroglycerin had bradycardia events. None of the bradycardia events among those treated with Natrecor were listed as "severe" in intensity.

Orthostatic blood pressures: No standing blood pressures were taken, no orthostatic values were available.

Tolerance: This study does not specifically address the issue of Natrecor tolerance or habituation. Nevertheless, the decrease in wedge pressures, among those treated with Natrecor over the 24 hour period for which most enrolled subjects successfully completed, was numerically better or

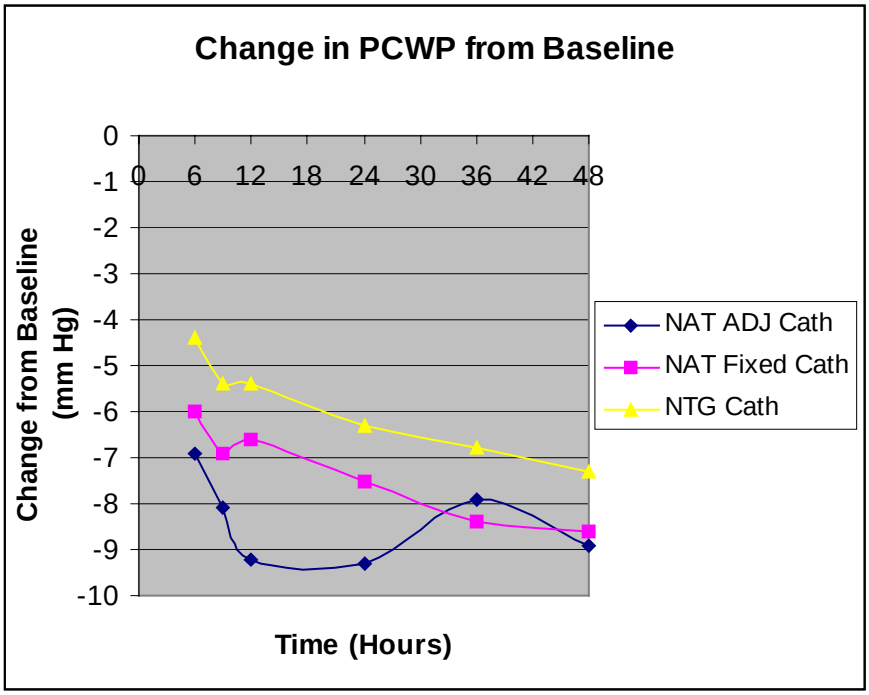
equivalent to those treated with NTG, despite an approximately 50% increase in the NTG infusion rate between 3-48 hours of the infusion. The worst that can be said is that any tolerance with Natrecor appears to be substantially less than tolerance observed with NTG.

Dose response: No dose response data can be derived from this study. The bolus dose was higher and the infusion rates lower than in previous studies of Natrecor.

Need for invasive hemodynamic monitoring: The effect on wedge pressure among those who were catheterized and those not catheterized is shown in Figure 17. The dose of Natrecor that was used among those catheterized and those Natrecor catheterized did not differ by much. The blood pressure drops paralleled the wedge pressure drops. The effect of the adjustable dose Natrecor was somewhat greater than that of the fixed dose. The safety data base among those treated with adjustable dose Natrecor was small. Only a small fraction of subjects were actually titrated to higher doses. Safety of the use of higher doses of Natrecor is better obtained from other studies, with larger databases.

It would appear that if one kept to fixed dose non-increasing doses of Natrecor, catheterization affords little benefit in either efficacy or safety.

Figure 17



Study summary: The VMAC study was a large multicenter study comparing the effects of Natrecor, nitroglycerin and placebo on both PCWP and dyspnea change in subjects with decompensated congestive heart failure. These patients on enrollment were to have dyspnea at rest, while supine or immediately upon modest activity such as eating or bathing.

Approximately 50% of those enrolled were to have the catheter inserted or if already catheterized to be allocated to the catheterized strata. The decision to place or not place a catheter was left to the discretion of the investigator. Those enrolled were to be randomized in a 1: 1: 1: 1: ratio to receive either Natrecor fixed dose: Natrecor adjustable dose : nitroglycerin : placebo. Those not catheterized were to be randomized in a 1: 1: 1 ratio of Natrecor fixed dose: Nitroglycerin: placebo. The treatment portion of the study consisted of two phases. The first three hours of the infusion were placebo-controlled. Subsequently, with the exception of placebo subjects, all subjects continued on their infusion regimen for at least a total of 24 hours. Those subjects randomized to placebo for the initial three-hours of the infusion were at the time of the initial randomized also allocated to receive either Natrecor fixed dose or nitroglycerin for the positive controlled portion of the study.

The Natrecor fixed dose consisted of a regimen of a bolus of 2 ug/kg over 60 seconds followed by a constant infusion of 0.01 ug/kg/min. This infusion regimen for Natrecor differs from that used in previous studies in that the bolus is larger and the constant infusion rates less. For the initial three-hour infusion the regimens for both the fixed and adjustable Natrecor doses were the same. After the initial placebo-controlled infusion, the dose of Natrecor among those in the adjustable dose cohort could have their dose increased. If the PCWP was > 20 mm Hg and the SBP > 90 mm Hg, the subject could receive a bolus of 1 mg/kg followed by an increase n the infusion rate of 0.005 ug/kg/min. The dose increased could be repeated but no more frequently than every three hours, predicated on the same wedge and systolic blood pressure criteria. The maximal infusion rate for the Natrecor adjustable dose was 0.03 ug/kg/min. Infusion of nitroglycerin is to be performed by the standard regimen of the investigator both through the three hour placebo-controlled and 24-hour positive –controlled phase.

The investigator was to be blinded with two infusions simultaneously administered through either different infusion sites or through a single site with "Y" connector. Each of the simultaneous infusions is to be assumed to consist of active drug.

The primary endpoints of the study were the effect of Natrecor when compared to placebo for PCWP at three hours for those catheterized and change in dyspnea symptoms at three hours for both catheterized and not catheterized patients. The prespecified plan was to pool the results of the Natrecor fixed and Natrecor adjustable dose regimens. Both PCWP and dyspnea change were to be demonstrate a statistical difference between placebo and pooled Natrecor doses (fixed and adjustable for hemodynamics and catheterized and not-catheterized for dyspnea change) at the three –hour time point, in order for the study to be considered successful.

Cardiac hemodynamics as well as change in dyspnea symptoms and the subject's global clinical status were also measured at 15 and 30 minutes and 1, 2 and 3 hours after the start of the infusion. PCWP and change in dyspnea and global score were recorded at all these time points. Other hemodynamic measurements (right atrial pressure, systemic vascular resistance, cardiac index, pulmonary vascular resistance and pulmonary artery pressure) were tabulated at baseline and 1 and 3 hours post dose.

For the positive controlled portion of the study PCWP was measured at 6, 9, 12 and 24-hours of the infusion and 36 and 48 hours of the infusion for those who were treated longer. Data

for other hemodynamics was collected at 24 hours. Symptom assessment both dyspnea change and global symptoms were collected at 6 and 24 hours and at the end of the infusion.

A total of 498 subjects were enrolled. The vast majority of subjects had their symptoms of heart failure as an exacerbation of their underlying disease. Only approximately 5% of those enrolled had their heart failure as a consequence of an acute myocardial infarction. A large portion of the population was substantially symptomatic of their CHF. Approximately 80% of those enrolled were NYHA Class III or IV at baseline. Rales and pedal edema were the most frequent symptoms and were present in approximately 70-75% of those enrolled. The protocol required patients to have dyspnea at rest for enrollment. At the time of the infusion, approximately 75% of those enrolled had symptoms either while sitting or lying flat or with one pillow.

Intravenous diuretics were used in approximately 50-70%, pressors, i.e., dobutamine, dopamine or PDE III inhibitors, were administered to 6-23%, 0-10%, and 0-6%, respectively during the 24-hours prior to the start of the infusion. After-load reducers, i.e. intravenous nitroglycerin, or nitroprusside were administered to 0-7% or 0-2%, respectively, during the same time period.

At the end of the three-hour placebo-controlled period, the placebo-subtracted effect of Natrecor (combined adjustable and fixed dose) was –3.8 mm Hg. The effect of Natrecor was highly statistically different from placebo ($p < 0.001$).

With respect to change in dyspnea Natrecor was only superior to placebo at the 3-hour measurement. The effect driven by the symptom benefit among those catheterized ($p=0.03$). There was no difference in comparing Natrecor to placebo, but the value at 3 hours was marginally in favor of Natrecor ($p=0.07$).

Wedge pressure effects of Natrecor relative to placebo was evident as early as 15 minutes (placebo-subtracted measurement was –2.3 mm Hg) after the start of the infusion. The effect remained relatively constant at –3.8 to -4.0 mm Hg after 0.5 hours.

Other hemodynamic measurements indicate an effect of Natrecor relative to placebo on right atrial pressure (decreased), systemic vascular resistance (decreased), cardiac index (increased), pulmonary vascular resistance (decreased) and mean pulmonary artery pressure at the earliest time point (1 hour). With the exception of systemic vascular resistance, all other metrics were statistically significant ($p< 0.05$) or marginally significant (cardiac index; $p=0.09$) at 3 hours.

Change in dyspnea score was assessed at the same time as the wedge pressure assessments. Patients in all treatment groups (even placebo) improved relative to baseline. Aside form the three hour time point (and largely driven by those catheterized), there was no differences between Natrecor and placebo.

During the initial three-hour infusion period, Natrecor was superior to nitroglycerin in decreasing wedge pressure at all time points with the exception of the two-hour time point. At the three-hour time point Natrecor produced a 2-mm Hg drop in wedge pressure greater than that produced by nitroglycerin. Other hemodynamic measurements were not significantly different from nitroglycerin, at three-hours, with respect to right atrial pressure, cardiac index, pulmonary vascular

resistance. Natrecor, however, did decrease mean pulmonary artery pressure when compared to nitroglycerin.

There were no differences between Natrecor and Nitroglycerin for change in dyspnea during this portion of the study.

After three hours, the placebo-treated subjects were switched to their randomized active treatment, the adjustable dose Natrecor dose could now be increased. Among those catheterized wedge pressures were measured at 6, 9, 12, 24, 36 and 48 hours. Other hemodynamic parameters were measured only at 24 hours. There were no differences between Natrecor fixed dose and nitroglycerin for any of these measurements.

On the other hand the Natrecor adjustable dose decreased wedge pressure to a greater extent than nitroglycerin at all time points through 24 hours. It also decreased right atrial pressures relative to nitroglycerin at 24 hours.

Despite the greater drop in wedge pressure of Natrecor adjustable dose relative to nitroglycerin, there was no benefit in dyspnea change.

There was no difference in urine output or weight change in comparing Natrecor adjustable or fixed to Nitroglycerin. Sodium excretion was not measured.

Natrecor's effect persists over the 24-hour infusion period and longer in a small proportion of subjects who were treated for > 24 hours, either with reference to baseline measurements or to the effect of increasing doses of nitroglycerin. These results suggest that over this duration of infusion tolerance is not a credible concern.

Hospitalization among those treated with Natrecor were approximately 2 days longer for the Natrecor treated group than the nitroglycerin group. Re-hospitalizations were equivalent between Natrecor and Nitroglycerin. Mortality at both 30 and 90 days and 6 months did not differ between the nitroglycerin and Natrecor (pooled fixed and adjustable) groups. The trend, however, favored nitroglycerin. The relative risk, comparing Natrecor to nitroglycerin at 30 and 90 days was approximately 1.5. At 6-months, the risk ratio still favored nitroglycerin but the risk ratio decreased to 1.11. There were few overall deaths at each time point and the confidence intervals for a mortality effect were therefore wide. The difference in the mortality effect is likely a s reflection of the "play-of-chance" and possibly related to the severity of disease at enrollment (i.e. need for pressors).

Several adverse events have been noted in previous studies with Natrecor. The dose employed in this study was less than those studies and consequently, the frequency and severity of such events appears to be less obvious. Hypotension was numerically more frequent but not statistically different in comparing Natrecor to nitroglycerin. The duration of these episodes was substantially longer among those treated with Natrecor than those treated with nitroglycerin.

Renal dysfunction appears to be more frequent among those treated with Natrecor. Group means of creatinine were slightly but not significantly higher among those treated with Natrecor.

The number of subjects with substantial increases in creatinine (> 0.5 mg/dL) was greater among those treated with fixed dose Natrecor (28%) than for Nitroglycerin (21%). The percent whose value was abnormal during the first week of treatment (9% versus 5%) and the percent still > 0.5 mg/dL at last measurement (14% versus 10%) was greater among those treated with fixed dose Natrecor.

Bradycardia as an adverse event was infrequently reported during this study. Through 14 days, bradycardia as an adverse event was reported in 4% of those treated with Natrecor and 1% of those treated with nitroglycerin. None of the bradycardia events among the Natrecor-treated subjects were “severe” in intensity.

This study supports the use of Natrecor at this low dose infusion rate of 0.01 ug/kg/min in subjects who are not catheterized and whose dyspnea can reliably be attributed to exacerbation of their CHF. This study by itself is insufficient to describe the effects of Natrecor as superior to that of nitroglycerine.

Protocol 704.329

Title of Study: Natrecor® (nesiritide) Versus Dobutamine Therapy for Symptomatic Decompensated CHF: A Safety Study Using 24-Hour Holter Monitoring

The PRECEDENT trial: Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy.

Investigator and Sites:

A total of 47 study sites enrolled subjects for this study (Table 50).

Table 50 Investigators and sites study # 704.329

Site # 546 John Boehmer, MD Milton S. Hershey Med. Center Hershey, PA	Site # 549 and # 602 D. Eric Bolster, MD Palmetto Clin Research Summerville, SC	Site # 352 Robert C. Bourge, MD U. of Alabama at Birmingham Birmingham, AL	Site # 561 Andrew Burger, MD Beth Israel Deaconess Med Cent. Boston, MA
Site # 550 James Carley, MD Cardiology Research Assoc Osmond Beach, FL	Site # 624 William Cotts, MD U of Iowa Hospitals and Clinics Iowa City, IA	Site # 620 Teresa DeMarco, MD U of California San Francisco Med Center San Francisco, CA	Site # 502 George Dennish III, MD San diego Cardiovascular Associates Encinitas, CA
Site # 618 Jay Dinerman, MD Jacksonville Heart Center PA Jacksonville Beach, Fl	Site # 379 Cra East, MD Baylor Univ Med Center Dallas, TC	Site # 554 Uri Elkayam, MD LA County-USC Med Center Los Angeles, CA	Site # 585 Lincoln Ford, MD Roudbush VA Med Center Indianapolis, IN
Site # 535 Winston Gandy, MD Saint Joseph Hospital of Atlanta Atlanta, GA	Site # 536 Jala Ghali, MD LSU Med Center Shreveport, LA	Site # 498 Michael Givertz, MD Boston Medical Center Boston, MA	Site # 538 Mitchell Greenspan, MD Lifemark Med Center Sellersville, PA
Site # 357 Joshua Hare, MD The Johns Hopkins Hosp Baltimore, MD	Site # 524 Edward Harlamert, MD Community Hosp. East Indianapolis, IN	Site # 635 and # 487 Paul J. Hauptman, MD Thomas Donohue, MD St. Louis Univ Med Center St. Louis, MO	Site # 355 Ray Hershberger, MD Oregon Health Sciences Univ Potland, OR
Site # 551 Peter Hoagland, MD Diego Cardiac Center San Diego, CA	Site # 306 Robert E. Hobbs, MD The Cleveland Clinic Foundation Cleveland, OH	Site # 382 Allen D. Johnson, MD Green Hospital of Scripps Clinic La Jolla, CA	Site # 356 Walter Kao, MD Rush-Presbyterian-St Lukes Med Center Chicago, IL
Site # 567 Ronald Karlsberg, MD Cardiovascular Research Inst Of Southern California Beverly Hills, CA	Site # 387 Stuart D. Katz, MD Columbia Presbyterian Med Center New York, NY	Site # 627 and #493 Michael Koren, MD W. Herbert Haught, MD Jacksonville Center for Clinical Research Jacksonville, FL	Site # 367 Marrick kukin, MD Mt Sinai Medixcal Center New York, NY
Site #369 Thierry LeJemtel Albert Einstein College of Med. Bronx, NY	Site # 605 Chang-seng Liang, MD, Ph.D. U of Rochester Med Center Rochester, NY	Site # 370 Charles Lui, MD U of Arizona Health Sciences Center Tucson, AZ	Site # 540 Stephen Mallon, MD U of Miami/Jackson Memorial Medical Center Miami. FL

Site # 413 and # 516 Frank McGrew, MD Baptist Clin Res Center Memphis TN	Site # 488 Carl Pepine, MD U of Florida Health Science Center Gainesville, FL	Site # 547 Steven Promisloff, MD Hillsboro Cardiology, PC Hillsboro, OR	Site # 628 Hanumanth Reddy, MD U of Missouri Hosp and Clinics Colombia, MO
Site # 622 Americo Simonini, MD Cedars Sinai Med Center Los Angeles, CA	Site # 626 Mara Slawsky, MD Boston VAMC Jamaica Plain, MA	Site # 560 Guillermo Torre-amione, MD, PhD Baylor College of Med Houston, TX	Site # 360 Jacob Varghese, MD George Washington U Med Center Washington, DC
Site # 625 William Wainwright, MD Jacksonville Heart Center, PA Jacksonville Beach, FL	Site # 539 David Wilson, MD U of Kansas Med Center Kansas City, KS	Site # 580 John R. Wilson, MD Vanderbilt U Med Center Nashville, TN	

Formulations:
Dobutamine was taken from the hospital formulary.
Natrecor (Lot # H0007A2) was produced by recombinant DNA Technology.

Dates of Study:
The protocol date: 9 April 1998
First subject was randomized: 15 August 1998
Last subject Randomized: 30 December 1998
Statistical protocol not dated.

Oversight Committees: There were no planned oversight committees.

Protocol: This study was divided into several phases:

- A screening phase
- Randomization
- A pre-treatment baseline Holter phase
- A on-treatment 24-hour infusion
- Post-treatment that extends from the end of the 24-hour period to 14 days.
- A 14-day mortality and hospitalization record.

Primary Analysis: The primary statistical analysis of this study is to compare the two Natrecor regimens to dobutamine with respect to heart rate and cardiac ectopy. The primary measures of interest are average heart rate and ventricular premature beats as well as average repetitive beats. Repetitive beats are defined as the sum of the number of beats contained in doublets, triplets and runs of VT. In addition the sponsor will tabulate the number of subjects who meet the criteria for defining a subject as having a proarrhythmic event as defined by Velebit[1], Morganroth[2] and CAPS[3].

[1] Velebit V, Podrid P, Lown B et al. "Aggravation and provocation o f ventricular arrhythmias by antiarrhythmic drugs" Circulation, 1982; 65 (5) 886-94
[2] Morganroth J, Michelson EL, Horowitz LN et al,"Limitataiion of routine long-term electrocardiographic monitoring to assess ventricular ectopic frequency" Circulation, 1978; 58 9e0 408-14
[3] The CAPS Investigators."The Cardiac Arrhythmc Pilot Study". Am J Cardiol, 1986; 57: 01-5.

The initial analysis will include all subjects receiving study drug and having both baseline and treatment Holter data. All data from the entire baseline and entire treatment period while he subject is receiving study drug as a single IV vasoactive agent and while on stable antiarrhythmic therapy will be included. The analysis is therefore bounded on the duration side by the 24-hour period of Holter observation but the treatment duration could be shortened if drug is discontinued or if antiarrhythmic treatment is initiated or the regimen changed.

A supplemental analysis will consider only the last 6 hours of baseline data as well as the first six-hour of treatment.

A subgroup analyses for heart rate will be those subjects whose predominant cardiac rhythm during the treatment Holter period is (or is not) an atrial rhythm.

If a between-group inferential strategy at an $\alpha = 0.05$ demonstrates a difference, then the individual groups will be compared at a level of $\alpha = 0.05$. If the global test is not significant at a $\alpha = 0.05$ level, then the treatments will be compared by the step-down method of Benjamini and Hochberg[4] will be used to compare treatment groups.

Quantitative endpoints will be normalized to unit time (minute or hour where appropriate). Variables will be evaluated as a change from baseline. These variables will be analyzed by a non-parametric Kruskal-Wallis test, followed by pairwise 2-sample Wilcoxon test.

Proarrhythmia by the criteria of Velebit, Morganroth or CAPS are binary (yes, no) outcomes. These will be analyzed by the generalized Fisher's exact test followed by pair-wise Fisher's Exact test. The incidence (presence/absence) of various arrhythmias will be evaluated within each treatment group using McNemar's test and between groups using the generalized Fisher's Exact test followed by pairwise Fisher's exact test.

Other statistical issues: There were no planned interim analyses, although the protocol allowed for the sponsor to perform analysis for corporate planning or regulatory review. One could conclude that the sponsor was not blinded to the treatments (i.e. dose of Natrecor) if such analyses were possible.

The omnibus F-test had a 74% -86% power to detect a 4 BPM difference with a SD of 8 BPM between groups. The range of power is dependent on the value of the intermediate treatment. For pairwise comparisons of ectopy, 100 premature ventricular beat (PVB) difference and a SD of 200 PVB/Hour, pairwise contrasts have an 83% power to detect differences.

Randomization and Blinding:

The study was open-labeled with respect to Dobutamine and Natrecor. The two doses of Natrecor were however blinded. Only subjects who successfully complete the 24-hour baseline Holter are to be randomized. At this point subjects will be randomized with the randomization stratified based on the baseline history of VT in a 1:1:1 ratio to dobutamine: Natrecor 0.015 ug/kg : Natrecor 0.03 ug/kg. Randomization is to occur as late as possible during the 24-hour Holter

[4] Benjamini Y and Hochberg Y. "Controlling the false discovery rate: a practical and powerful approach o multiple testing". J Royal Stat Soc, Series B, 1995; 57:289-300.

monitoring period. Aside from the on-site pharmacist, others at the study site are to remain blinded to the treatment assignment until the infusion is about to begin. The study drug is to be delivered to the bedside in a sealed, tamper-proof envelope. In the even that drug is not administered the sealed, unopened envelope is to be returned to the pharmacist.

The results of the Holter data are not to be disclosed either to the subject or investigator during the course of the study.

Inclusion Criteria: Subjects

- Are 18 years old
- Have a history of worse than or equal to NYHA Class III CHF
- Present with symptomatic, decompensated CHF for which in-subject therapy with either dobutamine or Natrecor administered with or without diuretics is deemed appropriate
- Are on stable doses of antiarrhythmics (>48 hours).

Exclusion criteria: Subjects are excluded if the subject:

- Is unable to tolerate either the washout period or the 24 hour Holter monitoring period without IV vasoactive medication support. Dobutamine, nitroprusside, nitroglycerin and dopamine must be withheld at least for 30 minutes prior to the baseline Holter.
- Has evidence of vascular instability or hypotension (e.g., SBP < 85 mm Hg, cardiogenic shock or evidence of hemodynamic instability requiring immediate inotropic support).
- Requires more than one vasoactive drug.
- Received more than 4 hours of treatment with dobutamine, milrinone, nitroprusside or IV NTG during this hospitalization.
- Required IV antiarrhythmic drug within during 48 hours before starting study drug.
- Serum K < 3.5 meq/L not corrected.
- Had a MI within 48-hours of initiation of study drug, unstable angina or ongoing cardiac ischemia.
- Had other cardiovascular disease (valvular stenosis, obstructive cardiomyopathy, constrictive pericarditis that might adversely respond to potent dilating agents.
- Sustained an arrhythmia i.e., VT or VF or cardiac arrest within seven days before study drug
- Had second or third degree heart block or whose AICD whose back up pacing is set at > 50 BPM.
- Had previous hypersensitivity to drugs that are to be used in this study.
- Participated in another investigational drug protocol.
- Is unlikely to Survive the 14-day observation period due to other medical condition.
- Cannot give informed consent or for whom compliance with follow-up procedures a likely to be a problem.

Doses:

Dobutamine: The dobutamine dose should begin with 5 ug/kg/min or may be titrated to this dose rapidly (within 1 hour). The dose may be increased but should not be decreased below 5 ug/kg/min during the first 24 hours, except as dictated by adverse events. The dobutamine, once stopped may be re-initiated, with the minimum dose set for 5 ug/kg/min

Natrecor: The two Natrecor regimens are constant infusions of either 0.015 ug/kg/min or 0.03 ug/kg/min. There is no bolus. The dose of Natrecor may be decreased or stopped due to symptomatic hypotension or if the systolic blood pressure falls to < 80 mm Hg. If Natrecor is stopped, the infusion may be restarted once the hypotension has resolved at an infusion rate of ½ that previously administered. The dose may be increased at intervals of no greater than every three hours and the dose precipitating the hypotensive episode should not be exceeded.

For subjects on Natrecor whose status worsens, the dose may be increased as appropriate but no more frequently than every three hours.

Concomitant therapy: IV and oral diuretics are not restricted. Morphine and non-intravenous cardiac medications are allowed.

There are no restrictions to medications post 24-hour Holter.

Procedures timing: The procedures and timing during the study are shown in Table 51.

Table 51. Timing of procedures in study 704.329

	Before Enroll-ment								Study days		
		0	15 min	30 min	3 Hr	8 Hr	16 Hr	24 Hr	2-7	8-9	10-14
Informed consent, Med History, Randomization	X										
Phys Ex, Height, Weight	X[5]										
CBC General chemistry	X[5]							X[6]			
Discontinue IV Meds[7]	X	X	→	→	→	→	→	X			
Holter	X[8]	X	→	→	→	→	→	X			
Clinical Signs and symptoms of CHF	X[9]				X			X			
Global Clinical Assessment					X			X			
BP and heart rate	X	X	X	X	X	X	X	X	X[10]		
Study drug administration		X	→	→	→	→	→	X[11 12 13]	X[12, 13]	X1[3]	
Na, K, CO2, Cl, Cr, BUN								X[14]			X
Na, K, Ca, Mg		X[15]									
Humoral factors (at selected sites)	X[16]				X			X			X
Adverse Events, deaths, re-admissions		X	→	→	→	→	→	→	→	→	X[17]

[5] Obtain within 36 hours of study drug.
[6] Obtain within 24-hour study drug termination or day 7 whichever occurs earlier.
[7] As per protocol
[8] Obtain baseline Holter of 24 hours with recording to stop no earlier than 30 minutes before study drug infusion is started.
[9] Obtain within six ours of study dug
[10] Monitor per usual at this point
[11] Administer as a single IV agent
[12] Can continue Natrecor through day 7
[13] Dobutamine infusion is to be determined by the principal investigator
[14] I f study drug is used more than 24 hours obtain 24 hours during the start of the study drug
[15] Record any additional values during the 24 hour treatment period.
[16] Obtain within 1 hour of study drug
[17] Record all such events through day 14/

Results:

Demographics: A total of 255 subjects were enrolled into this study. The demographic characteristics of those are shown in Table 52.

Table 52 Demographics of patients enrolled into study 704.329

	Dobutamine (n=86)	NAT 0.015 ug/kg/min (N=85)	NAT (0.03 ug/kg/min) (N=84)	p-value
Age (mean ± SD)	62 ± 14	60 ± 14	61 ± 14	0.9
Ethnicity				0.9
White	48 (56%)	47 (55%)	41 (49%)	
Black	25 (29%)	23 (27%)	23 (27%)	
Hispanic	11 (13%)	13 (15%)	16 (19%)	
Asian	2 (2%)	0 (0%)	2 (2%)	
Missing		2(3%)		
Gender M/F (% M)	54/32 (63%)	58/27 (68%)	58/26 (69%)	0.6
NYHA III/IV (% IV)	55/31 (36%)	68/17 (20%)	65/19 (23%)	0.04
Treated subjects as random	N=83	N=84	N=79	
CHF History				0.3
Ischemia	42 (49%)	44 (52%)	44 (52%)	
Idiopath dilated cardiomy	22 (26%)	13 (15%)	24 (29%)	
Hypertensive	10 (12%)	14 (16%)	6 (7%)	
# not included	10 (12%)	13 (14%)	5 (6%)	
Cardiovascular history:				
Previous MI	37 (45%)	43 (51%)	46 (58%)	0.2
Hypertension	54 (65%)	56 (67%)	51 (65%)	0.96
Arrhythmia History				
AF or AF/Fl	29 (35%)	18 (21%)	21 (27%)	0.1
NSVT	25 (30%)	22 (26%)	19 (24%)	0.7
Sustained VT	7 (8%)	7 (8%)	5 (6%)	0.9

The groups overall were balanced. The dobutamine group, however, had a greater fraction of those enrolled having NYHA Class IV heart failure than either of the two Natrecor groups. The most common cause of disease was ischemic heart disease.

Dose: The study was carried out as planned. The duration of infusions is shown below.

Table 53 Duration of infusion study 704.329

	Dobutamine (n=83)	Natrecor	
		0.015 ug/kg/min (n=84)	0.03 ug/kg/min (n=79)
# terminated at < 22 Hrs	6 (7%)	4 (5%)	11 (14%)
# whose dose ≥ planned	3 (4%)	2 (2%)	6 (8%)
# whose dose < planned	3 (4%)	2 (2%)	5 (6%)
# dosed ≥ 22 Hrs.	77 (93%)	80 (95%)	68 (86%)
# whose dose ≥ planned	63 (76%)	61 (73%)	48 (61%)
# whose dose < planned	14 (17%)	19 (23%)	20 (25%)
AE as reason for premature termination	6 (7%)	4 (5%)	11 (14%)
Reason dose decreased to < minimum			
AE	14 (17%)	21 (25%)	23 (29%)
Other	6 (7%)	10 (12%)	13 (16%)
# Subjects with dose > minimum		2 (2%)	3 (4%)

Duration of Natrecor Infusion excluding interruptions is shown in Table 54. The time at each dose level are shown in Table 55.

Table 54 Duration of infusions excluding interruptions.

	Dobutamine (n=83)	Natrecor 0.15 ug/kg/min (n=84)	0.03 ug/kg/min (n=79)
Time of infusion mean ± SD (Hrs)	52.0 ± 40	38.7 ± 28	36.7 ± 33
Median (25-75%) (Hrs)	33 (24-71)	24.1 (24-44)	24.1 (24-44)
< 1 Hr	0	0	0
1 to <3	1 (1%)	0	1 (1%)
3 to <6	3 (4%)	2 (2%)	4 (5%)
6 to <22	2 (2%)	5 (6%)	10 (13%)
22 to < 26	31(37%)	51 (61%)	38 (48%)
26 to < 48	14(17%)	7 (8%)	9 (11%)
48 to < 72	13(16%)	9 (11%)	9 (11%)
> 72	19(23%)	10 (12%)	8 (10%)

Table 55 Through 22 hours, the number of hours at each dose level. (Mean ± SD)

Dose Range (ug/kg/min)	Dobutamine		Dose Range (ug/kg/min)	Natrecor	
				0.015 ug/kg/min	0.03 ug/kg/min
0 (study drug interrupted/stopped)	0.1 + 0.5		0 (study drug interrupted/stopped	0.3 + 1.2	0.9 + 2.8
>0 to <4.0	1.6 + 4.9		>0 to 0.01125	2.1 + 5.0	0 + 0
>4.0 to 6.0	17.8 + 7.7		>0.01125 to 0.0225	19.2 + 6.0	2.3 + 5.25
> 6.0	1.0 + 4.1		0.0225 to 0.0375	0.0 + 0.1	16.9 + 7.6
			>0.0375	0	0.1 + 0.7

For the dobutamine group, 1.7 of the 22 hours the infusions were at doses < 80% the proposed target dose. For the Natrecor 0.015 ug/kg/min dose, subjects spent 2.4 hours of the 22 hours examined at < 75% of the targeted dose. With respect to the Natrecor 0.03 ug/kg/min dose subjects spent 3.2 hours at < 75% of the targeted dose.

Concomitant medications: The percent of subjects in each group taking medication are shown in Table 56. The medication lists consists of the % subjects taking medication chronically (CHRNC) and during the 24 hour baseline Holter phase (B'LINE) and during the active infusion phase (INFUS). There were no great differences either between groups or during the three phases of the study.

With respect to types of medications commonly used for heart failure, the vast majority of subjects were on some form of diuretics, but there is no description as to whether the diuretics were oral or intravenous. ACE-inhibitors were taken by approximately 60-70% of the subject population and AII blockers in 7-16% of the population. Beta-blockers were less frequently used (10-25% of those enrolled). 20-29 % of those enrolled was treated with Statins. There was no line listing for spironolactone. The medication profile among those who had a history of VT at baseline did not substantially differ from the group as a whole. Class III antiarrhythmic drugs were used slightly higher frequency 25% for those with VT at baseline versus 7-16% for the population as a whole.

Table 56 Percent subjects taking class of medication (CHRNC)= chronic use of class before study; (B'LINE)= Baseline Holter pre-infusion period; (INF) infusion period.

	Dobutamine (% pts)			Natrecor 0.015 ug/kg/min			Natrecor 0.03 ug/kg/min		
	CHRNC	B'LINE	INFUS	CHR	BL	INF	CHR	BL	INF
Dobutamine	0	0	0	0	0	0	0	0	1
PDE inhibitors	0	0	0	0	0	0	0	0	0
Nitrates	42	51	52	38	35	35	49	47	43
IV NTG	0	0	0	0	0	0	0	0	0
Nitroprusside	0	0	0	0	0	0	0	0	0
Dopamine	0	0	0	0	0	1	0	0	0
Pressors	0	0	0	0	0	0	0	0	0
Diuretics	93	92	87	90	92	92	96	95	91
Digoxin	75	73	80	73	73	75	75	76	75
ACE inhibitors	70	70	71	71	74	70	70	68	63
Hydralazine	8	10	12	8	8	8	10	10	9
Class III antiarrhythmics	16	16	14	8	6	7	14	11	14
Beta blockers	25	22	22	25	23	20	18	10	11
Ca Channel blockers	14	11	8	15	8	10	14	9	9
Other antiarrhythmics	2	5	4	1	4	1	1	5	5
Other antihypertensives	2	4	5	7	7	6	6	6	6
AII receptor blocker	16	14	12	11	10	7	13	11	9
Warfarin	34	22	29	19	20	21	33	16	20
Low Mol Wt Heparin	1	5	5	6	5	6	0	3	3
Heparin	0	10	12	0	14	17	3	10	11
Aspirin	41	42	43	58	61	60	46	49	52
IIb/IIIa inhibitors	0	0	0	1	2	2	0	0	0
Stains	29	29	29	21	20	23	28	20	20

Interventions of note during the 24-hour infusion:

Dobutamine:

- one dobutamine subject had a new antiarrhythmic added.

NAT 0.015 ug/kg/min

- one subject had new antiarrhythmic medication added and
- one subject required dopamine.

NAT 0.03 ug/kg/min

- one subject was placed on IV vasoactive medication and
- one subject had their antiarrhythmic drug-dosing regimen altered.

Efficacy end points:

Quality of data: The quality of the data in general appears good. The vast majority of subjects had Holters of duration of > 22 hours with > 90% of the Holters interpretable both at baseline and during treatment. Where data is missing there did not appear to be a bias for missing data in any treatment.

The baseline values for heart rate and ectopy (PVBs and average repetitive beats) are shown in Table 57. The groups are reasonably well matched at baseline. The distribution of ectopy is however skewed with marked differences between mean and median values.

Table 57 Baseline measurements of heart rate and ectopy

		Natrecor ug/kg/min		
	Dobutamine (N=83)	0.015 (N=84)	0.03 (N=79)	Nominal p-value (stratified Van Elteren procedure controlled for VT status)
Average heart rate				
Mean ± SD	83 ± 17	82 ± 15	85 ± 14	0.6
Median (25-75%)	82 (73-96)	81 (72-91	84 (76-93)	
Average PVBs				
Mean ± SD	192 ±338	110 ± 170	165 ± 265	0.3
Median (25-75%)	39 (13-338)	35 (5-145)	50 (8-200)	
Average hourly repetitive beats				
Mean ± SD	30 ± 102	14 ± 36	23 ± 58	0.3
Median (25-75%)	1 (0-8)	1 (0-5)	1 (0-12)	

The effect of treatment on baseline is shown in Table 58. Dobutamine increases average heart rate as well as hourly PVBs and hourly repetitive beats.

Table 58 Changes in values from baseline

		Natrecor ug/kg/min		
	Dobutamine (N=83)	0.015 (N=84)	0.03 (N=79)	Nominal p-value (stratified Wilcoxon procedure controlled for VT status)
Average Heart Rate (Holter)				
Mean ± SD	5 ± 8	-1 ± 6	1 ± 7	<0.001
Median (25-75%)	4 (-2- + 10)	-1 (-5 -+3	1 (-3 -+ 5)	
p-value versus dobutamine		<0.001	0.002	
Average hourly PVBs				
Mean ± SD	69 ±214	-13 ± 83	-5 ± 96	0.001
Median (25-75%)	4 (-7- +107)	-1 (-24- +3)	-1 (-29 -+5)	
p-value versus dobutamine		0.001		
Average hourly repetitive beats				
Mean ± SD	15 ± 53	-5 ± 19	3 ± 34	<0.001
Median (25-75%)	0 (0-+7)	0 (-2-0)	0 (-2-0)	
p-value versus dobutamine		<0.001	0.001	

Heart rate: Based on the Holter tapes there was a average increase from baseline in heart rate of 5 BPM in the dobutamine group and essentially no change among those treated with Natrecor. This difference was highly significant. Not surprisingly, the time in tachycardia (HR > 100) was substantially longer for dobutamine then either of the Natrecor doses. The time in bradycardia was substantially reduced by dobutamine to a greater extent than was reduced by either of the two Natrecor doses (this was a secondary end point).

Table 59 Holter time in tachycardia and bradycardia

	Dobutamine (N=83)	Natrecor (ug/kg/min)		p-value
		0.015 (N=83)	0.03 (N=79)	
Baseline time in tachycardia (Hrs)	4.0 ± 6.3	3.7 ± 6.8	3.2 ± 5.6	0.8
Baseline time in bradycardia	2.3 ± 5.4	2.0 ± 4.8	1.7 ± 4.9	0.6
Change in Time in Tachycardia (Hrs)				
Mean ± SD	1.7± 5.3	0 ± 4.2	0.8 ± 3.5	0.044
Median (25-75%)	0 (0- + 2.3)	0 (-0.4 -+0.1)	0 (-0.2 –+1.1)	
p-value versus dobutamine		0.02	0.4	
Change in time in bradycardia (Hrs)				
Mean ± SD	-1.3 ± 3.4	0.3 ±2.8	-0.2 ±2.6	<0.001
Median (25-75%)	0 (-0.6-0)	0 (0- +0.1)	-0 (0-0)	
p-value versus dobutamine		<0.001	0.02	

Premature Ventricular Beats: There was a substantial increase in the mean and a smaller increase in median PVB relative to baseline for those receiving dobutamine. There was essentially no change or perhaps a small decrease among those treated with Natrecor See Table 58, above).

Changes in Average Hourly repetitive beats. Mean baseline values show modest differences between the three treatment groups, with the dobutamine having numerically more repetitive beats/ hour than the two Natrecor groups (table 58). The change from baseline shows a significant increase in repetitive beats/hour for the dobutamine group relative to either of the two Natrecor regimens.

With respect to specific ventricular ectopy i.e., couplets, triplets and VT beats, there was an increase in all measurements of ectopy in the dobutamine treated group relative to the Natrecor groups.

Table 60 Ectopy and change in ectopy from baseline Holter measurements

	Dobutamine (N=83)	Natrecor (ug/kg/min)		p-values (overall)
		0.015 (N=84)	0.03 (N=79)	
Couplets (events/24 Hr)				Baseline
Mean ± SD (Baseline)	310 ± 1008	139 ± 372	228 ± 561	0.3
Median (25-75%)	12 (2- +83)	5 (1-59)	9 (1- +133)	
Change from baseline				Change
Mean ± SD	+68 ± 427	-52 + 200	38± 317	0.001
Median (25-75%)	+ 2 (-3 -+ 41)	-1 (-17 - + 1)	0 (-7- + 4)	
p-value relative to dobutamine		<0.001	0.0080	
Triplets (events/24 Hr)				Baseline
Mean ± SD (Baseline)	27 ± 129	10 ± 33	20 ± 61	0.3
Median (25-75%)	0 (0-+3)	0 (0-+2)	1 (1-133)	
Change from baseline				Change
Mean ± SD	+22 ± 86	-5 ± 15	3 ± 38	<0.001
Median (25-75%)	+ 0 (0 -+ 2)	0 (-1 - + 0)	+0 (-1- + 0)	
p-value relative to dobutamine		<0.001	0.0080	
VT (events/24 Hr)				Baseline
Mean ± SD (Baseline)	30 ± 144	13 ± 39	27 ± 89	0.2
Median (25-75%)	0 (0-+5)	1 (0-+3)	1(0-+8)	
Change from baseline				Change
Mean ± SD	+48 ± 205	-6 ± 17	2 ± 60	<0.001
Median (25-75%)	+ 0(+0- +3)	+0 (-2 - + 0)	0 (-1- + 0)	
p-value relative to dobutamine		<0.001	<0.001	

The number of subjects with no VT events at baseline who developed VT and the number of subjects with VT at baseline whose VT events were not evident during on-treatment Holters are shown in Table 61.

Table 61 New onset or disappearance of VT events on treatment.

	Dobutamine (N=83)	Natrecor (ug/kg/min)			Dobutamine (N=83)	Natrecor (ug/kg/min)	
		0.05 (N=84)	0.3 (N=79)			0.05 (N=84)	0.3 (N=79)
VT absent on baseline tape				VT present on baseline tape			
Absent → Present	11 (15%)	7 (9%)	6 (8%)	Present → Absent	4 (5%)	12 (15%)	8 (11%)
Absent → Absent	24 (33%)	28 (35%)	22 (31%)	Present →Present	34 (47%)	33 (41%)	36 (50%)

(Comment: the number of subjects does not sum to those enrolled. For dobutamine only 73/83 subjects are accounted for in this table. For Natrecor 0.015 ug/kg/min the number 80/84 have data, for Natrecor 0.03 ug/kg/min 72/79 have data. The reason for the discrepancy is not stated).

The overall p-value (based on a CMH general association statistic controlling over baseline VT (present or absent) of Natrecor relative to dobutamine showed a nominal p-value for the 0.015 ug/kg/min regimen of 0.039 and for the 0.03 ug/kg/min the nominal p-value was 0.191. (Comment: The p-values were not corrected for multiple comparisons).

Proarrhythmia: Several criteria have been used that define a subject as having a pro-arrhythmic episode.

The sponsor only analyzes the criteria based on the Velebit and The CAPS criteria.

Table 62 Proarrhythmia events based on criteria of Velebit and CAPS

	Dobutamine	Natrecor (ug/kg/min)		Overall p-values
		0.015	0.03	
Velebit Criteria:				
Proarrhythmia: yes	17 (23%)	3(4%)	0	<0.001
No	56 (77%)	77 (96%)	72 (100%)	
p-value versus dobutamine		<0.001	<0.001	
CAPS Criteria:				
Proarrhythmia: yes	7 (10%)	0(0%)	0	0.001
No	66 (90%)	80 (100%)	72 (100%)	
p-value versus dobutamine		0.005	0.013	

[Comment: The numbers also don't add up to those enrolled.]

Global assessment of clinical status: At 3 and 24 hours, both the subject and the investigator were asked to evaluate their clinical symptom change relative to baseline. A five-point scale was used: Markedly better, better, no change, worse and markedly worse. There was no difference in evaluations in considering either the subject or investigator's responses (both are listed in Table 63).

Table 63 Assessment of symptom score

	Subject				Investigator			
	Dobut	Natrecor (ug/kg/min)		p-value nominal K-W	Dobut	Natrecor (ug/kg/min)		p-value nominal K-W
		0.015	0.03			0.015	0.03	
3 Hours								
Markedly Better	3 (4%)	1 (1%)	0	0.5	1(1)	0	0	0.7
Better	23 (29%)	30 (38%)	26 (34%)		25(31%)	25 (32%)	21 (27%)	
No change	49 (61%)	45 (58%)	48 (62%)		53 (66%)	51 (65%)	54 (70%)	
Worse	5 (6%)	2 (3%)	2 (3%)		1 (1%)	2 (3%)	1 (1%)	
Markedly worse	0	0	1 (1%)		0	0	1 (1%)	
p-value Vs. DOB		0.3	0.9			0.8	0.4	
p-value Vs. NAT low dose			0.4				0.5	
24 Hours								
Markedly Better	12 (15%)	13 (16%)	8 (11%)	0.2	5 (6%)	8 (10%)	4 (5%)	0.1
Better	56 (68%)	55 (66%)	47 (63%)		63 (77%)	61 (73%)	48 (66%)	
No change	13 (16%)	13 (16%)	14 (19%)		12 (15%)	14 (17%)	16 (22%)	
Worse	1 (1%)	2 (2%)	6 (8%)		2 (2%)	1 (1%)	5 (7%)	
Markedly worse	0	0	0		0	0	0	
p-value Vs. DOB		0.98	0.1			0.7	0.1	
p-value Vs. NAT low dose			0.1				0.1	

Subject's status improved over time as judged either by the subject or the investigator's assessment. There did not appear to be a benefit of either treatment or either dose of Natrecor.

Safety:

Exposure: The median duration of exposure for dobutamine and the two Natrecor doses are shown in Table 54. The number of subject*days for the three treatment groups were 180 for the dobutamine cohort, and 135 for the Natrecor 0.015 and 121 for the Natrecor 0.03 ug/kg/min infusion regimens.

Deaths/Dropouts/ Discontinuations: The protocol prespecified a 14-day follow-up. There were a total of 7 deaths during the initial 14-day follow up, period; 2 in the dobutamine and NAT 0.015 groups and 3 in the NAT 0.03 group. In addition the sponsor collected the number of subjects who died during the one-month and six months following treatment. The results for the 1 and 6-month follow up are shown in Table 64. There were some differences in baseline with more dobutamine classified as Class IV subjects than either of the two Natrecor cohorts.

Capsular summaries for those who died during the pre-specified 14-day follow-up are supplied by the sponsor and are summarized below.

Table 64 Deaths at one and 6 months

	Dobutamine (n=83)	Natrecor 0.015 ug/kg/min (n=84)	Natrecor 0.03 ug/kg/min (n=79)
1 month			
Deaths	5	3	3
Mortality rate	6.1%	3.6%	3.8%
95% C.I. (Peto's)	2.2 to 12.6%	1.0 to 9.3 %	1.0 to 9.8%
p-Value (versus dobutamine)		0.5	0.5
p-Value Nat low versus NAT high		-------	0.94
Censored before 1 month (%)	1 (1%)	2 (2%)	1 (1%)
6 month			
Deaths	18	13	13
Mortality rate	22.2%	15.9%	16.7%
95% C.I. (Peto's)	13.8 to 31.8%	8.9 to 9.3 %	1.0 to 9.8%
p-Value (versus dobutamine)		0.3	0.4
p-Value Nat low versus NAT high		-------	0.9
Censored before 1 month (%)	3 (4%)	3 (4%)	2 (3%)

There were numerically more deaths on dobutamine then on either of the Natrecor doses at both 1 and 6 months. Capsular summaries of those who died within 14-days of the infusion are summarized below.

Dobutamine

Subject # 502-215: This was a 93-y/o male with NYHA Class IV CHF as a consequence of ischemia. He was treated for 3.5 hours with dobutamine but was discontinued due to symptomatic hypotension. The event resolved but the subject remained hospitalized and died on day 8.

Subject # 536-214: This was a 78-y/o female with NYHA Class IV CHF. She was treated for approximately 4 hours with dobutamine that was stopped because the subject experienced multiple arrhythmias, not seen during baseline. The subject's ectopy resolved after approximately 30 minutes. She was discharged on day 2 but died on day 7 of a cardiopulmonary arrest.

NATRECOR (0.015 ug/kg/min).

Subject # 554-211: This was a 60-y/o male with NYHA Class III CHF who was treated for 22 hours with Natrecor (0.015 ug/kg/min) with the infusion stopped due to symptomatic (dizziness) hypotension (BP 68/38). His creatinine increased from 1.4 at baseline to 1.9 at day 2. He had an episode of AV block that lasted 60 seconds but resolved spontaneously. His K+ level rose to 7.5 mg/dL on day

6. No follow-up creatinine values were supplied. He was found unresponsive while still hospitalized (day 8). He had new onset atrial fibrillation and a junctional rhythm. He was intubated but arrested and died.

Subject # 618-206: This was a 59-y/o male NYHA Class III who was treated for 24 hours with study drug, with the infusion stopped because of clinical improvement. Nine hours after the start of study drug infusion, the subject experienced an episode of asymptomatic NSVT. The subject was discharged on day 2 but arrested and died on day 14.

NATRECOR (0.03 ug/kg/min)

Subject # 498-203 was a 44-y/o male with NYHA Class III. He was treated for 7.5 hours with NAT (0.03 ug/kg/min) with the infusion discontinued due to symptomatic hypotension (SBP decreased from 98 mm Hg at baseline to 74 mm Hg at 6 hours 53 minutes). The subject was discontinued from the infusion. A Swan-Ganz catheter was inserted demonstrating elevated right and left filling pressures and marked hypo-perfusion. He was treated with Nipride and improved. He was discharged on day 13 but died that evening at home. An autopsy was performed but the results were not included in the summary.

Subject # 551-205 is a 67-y/o male with NYHA Class IV CHF. On admission the subject had severe edema, paroxysmal nocturnal dyspnea and SOB. The subject was treated for 4.5 days with Natrecor, with the infusion discontinued because the physician believed the subject had received maximum benefit. The subject had originally been admitted for hip surgery and after the completion of the infusion the subject was taken to the operating room. The subject had two short episodes of bradycardia during the NAT infusion. On day 6 post-op, he was found unresponsive and died despite resuscitative efforts.

Subject # 352-203 was a 54-y/o male NYHA class III CHF who was admitted with volume overload and underwent diuresis. His BUN/Cr on admission were 71/2.4 mg/dL respectively. The dose of Natrecor was increased to 1.5 times the initial dose. IV diuretics were also administered but any diuresis was not sustained. Natrecor was discontinued and dobutamine and later dopamine was started. On day 10, chronic continuous dialysis was started. On day 12 he developed symptomatic bradycardia and hypotension and arrested. He was resuscitated with bradycardia and hypotension persisting on day 14. He died on day 19.

Serious adverse events: Excluding those who died, serious adverse events are summarized below:

Dobutamine:

Subject # 356-201 was a 61-y/o male with NYHA class II status due to ischemic cardiomyopathy. He was treated with dobutamine for 5 days. He was electively admitted for the placement of a LVAD on day 13 and is awaiting a heart transplant.

Subject # 413-201 was a 62-y/o female with NYHA class II CHF with a history of paroxysmal VT. She was treated for 24 hours and then discharged. On day 10 she was readmitted with worsening CHF and treated with milrinone, Lasix and oxygen for 24 hours and then discharged. She was again admitted on day 14 for worsening shortness of breath and was treated with milrinone and oxygen for 10 hours before discharge.

Subject # 502-206 was a 61-y/o female NYHA class III CHF due to ischemia, She was treated for 36 hours with dobutamine which was discontinued due to clinical improvement. She was readmitted for substernal chest pain on study day #7, treated with NTG and observation.

Subject # 536-213 was an 87-y/o female with NYHA Class IV was treated for 24 hours with dobutamine. The infusion was discontinued due to clinical improvement. She was discharged on day 3 but readmitted on day 5 for worsening CHF and was discharged on day 7.

Subject # 551-206 was a 74-y/o male with NYHA class III he was treated for 2 days with dobutamine and discharged from the hospital on day 7. On day 10 the subject was readmitted for increased shortness of breath. He was treated with Bumex and was discharged on study day 12. He had an elective lung biopsy that confirmed the diagnosis of lung cancer. He was readmitted for placement of a chest tube to treat the pneumothorax. He was discharged on day 21.

Subject # 560-213 was a 59-y/o male with idiopathic dilated cardiomyopathy and NYHA Class III who was treated for 24 hours with dobutamine. The subject's hospitalization was prolonged due to hyperglycemia and hyperkalemia. He was treated with insulin and Kayexalate and discharged on study day # 4.

Subject # 585-201was a 55-y/o male with NYHA Class III CHF who was treated for 24 hours with dobutamine. He was discharged on day 3 but readmitted on day 4 for worsening CHF.

NATRECOR 0.015 ug/kg/min

Subject # 369-205 was a 60-y/o male NYHA Class III and a history of ischemic cardiomyopathy that was treated for approximately 24 hours. The infusion was discontinued because the patient had low cardiac output. Dobutamine was started. The subject was discharged on day 4 but readmitted on day 8 for low cardiac output. He was treated with dobutamine and discharged on day 11.

Subject # 498-202 was an 82-y/o female with a history of ischemic cardiomyopathy, NYHA class III was treated with 24 hours with Natrecor that was stopped due to clinical improvement. On day 5 she was noted to have a UTI. She was transferred to a cardiac rehabilitation facility on day 6. Her creatinine and BUN began to rise and she was readmitted. By study day 14, her creatinine and BUN were improving and she was discharged. Renal function parameters re-approached those measurements of baseline.

Subject # 502-202 was an 83-y/o female with NYHA class III status due to severe mitral regurgitation. She was treated for 4 days with Natrecor that was discontinued due to clinical improvement. On day 6, due to shortness of breath and pulmonary edema she was treated with dobutamine with no response. A mitral valve replacement was scheduled (the subject had a history of mitral regurgitation). On day 9, she required dialysis for worsening renal insufficiency. Mitral value replacement was performed on day 10.

Subject # 502-210 was a 68-y/o male with NYHA class IV CHF who was treated for 24 hours with Natrecor. The infusion was discontinued due to clinical improvement. He was discharged on day 2. Over the next 12 days the subject had worsening symptoms and was admitted on day 14 for exacerbation of CHF and was treated with dobutamine. On day 15, he experienced a cardiac arrest after an episode of VT. He was resuscitated and discharged on day 18 in stable condition.

Subject # 538-203 was a 69-y/o female with NYHA class III CHF and a past history of cerebrovascular accident. Four hours during the infusion, the subject developed aphasia and facial droop. Her blood pressure had decreased from 135/65 to 99/54 (not defined as hypotension). The subject was started on heparin and shortly thereafter, the subject developed symptomatic hypotension (BP-74/43). Dopamine was started and the Natrecor infusion interrupted. The SBP rose slightly to 91/38. Natrecor was restarted at half the infusion regimen. The aphasia resolved. A CT scan done on day 7 demonstrated a right occipital CVA.

Subject # 605-207 was a 73-y/o female who was treated for 24 hours with Natrecor and discharged on day 3 but readmitted on day 10 with exacerbation of CHF. During this admission she had intractable hypertension. A renal ultrasound revealed bilateral renal artery stenosis. She subsequently underwent bilateral renal artery angioplasty and stent placement. She was hospitalized for 2 weeks before discharge.

Subject # 370-202 was a 70-y/o male with NYHA class IV CHF due to ischemic cardiomyopathy. He was treated for 8 days with Natrecor and discharged. He was readmitted on day 13 due to shortness of breath. He was treated with Lasix and discharged the following day.

Subject # 382-201 was an 81-y/o female with NYHA class III who was treated with infusion for 24 hours with Natrecor. She was admitted on day 13 for increasing disorientation, weakness and dizziness associated with her baseline condition of anemia and also attributed to CHF. She was treated with IV Lasix and two units of packed red blood cells. She was discharged on day 17.

Subject # 536-219 was a 37-y/o male with NYHA class III due to alcohol-induced cardiomyopathy and also a history of NSVT. He was discharged on day 3 but readmitted on day 7 with worsening of shortness of breath. He was discharged on day 9.

Subject # 536-220 was a 62-y/o male with NYHA class III due to amyloidosis that was treated for 24 hours with clinical improvement. During the course of the infusion the dose of Natrecor was decreased because of symptomatic hypotension (BP 72/50). He was discharged on day 3. When seen on day 11 in clinic he had an increases in shortness of breath and also elevations of his BUN /Cr (90/3.2, respectively). He was admitted on day 14 for scheduled inotropic therapy. [Comment: Patient with restrictive cardiac disease tolerated infusion.]

Subject # 560-209 was a 67-y/o female NYHA class III was treated for 24 hours with Natrecor with the infusion discontinued due to clinical improvement. On day 8 she was readmitted for worsening CHF. A mitral valve repair was unsuccessful on day 16 so valve replacement was performed. The subject was discharged from the hospital on study day 28.

Subject # 620-204 was a 78-y/o male with NYHA class III CHF who was treated with study drugs for 3 days with the infusion stopped because of clinical improvement. He was discharged on day 7 but was readmitted on day 11 due to worsening anemia. He was treated with several transfusions of packed red blood cells and discharged on day 19.

Adverse Events with Intensity Listed as "severe". Adverse events with intensity labeled as "severe". The events labeled as "severe" in intensity are shown in Table 61. More subjects treated with Natrecor 0.03 ug/kg/min had such events than the lower dose Natrecor or the dobutamine group.

Premature terminations: 21 subjects prematurely terminated (before 22 hours of infusion). These subjects consisted of 6 dobutamine, 4 NAT 0.015 ug/kg/min and 11 NAT 0.03 ug/kg/min subjects. The sponsor tabulates specifics of the early termination that are reproduced in Table 66. The most common causes of premature for those treated with dobutamine were related to ectopy. The most common causes for those treated with Natrecor were episodes of hypotension.

Table 65 Events "severe" in intensity (through day 14).

Pt #	Tx	Demographics: Age/Race/Gender/NYHA	Event
369-206	DOB	35/B/F/IV	Fever
502-215	DOB	93/C/M/IV	Symptomatic hypotension, bilateral tibial edema,Cheyne-Stokes respiration, agitation, severe bradycardia.
536-214	DOB	78/B/F/IV	Cardiopulmonary arrest
551-206	DOB	74/C/M/III	Increased shortness of breath
560-213	DOB	59/B/M/III	Worsening hyperkalemia, hyperglycemia
560-216	DOB	43/B/F/IV	Worsening renal function, abdominal pain
561-201	DOB	69/C/M/III	Chest pain, angina
369-205	NAT 0.015	60/H/M/III	Worsening CHF
502-202	NAT 0.015	83/C/F/IV	Increasing creatinine, BUN, symptomatic hypotension, pulmonary edema
502-205	NAT 0.015	77/C/M/III	Headache, anxiety
502-210	NAT 0.015	68/Pac Is/M/IV	Worsening CHF
502-211	NAT 0.015	63/C/M/III	Cold sweat, non-symptomatic hypotension
524-201	NAT 0.015	57/C/M/III	Symptomatic hypotension
540-201	NAT 0.015	64/C/M/IV	Fatigue
554-211	NAT 0.015	60/H/M/III	Worsening CHF, asystole, cardiac arrest
605-207	NAT 0.015	73/B/F/III	Renal artery stenosis
618-206	NAT 0.015	59/B/M/III	Acute MI
306-203	NAT 0.030	76/C/F/IV	Hyperkalemia, dehydration
352-203	NAT 0.030	53/C/M/III	Worsening CHF, worsening renal failure, symptomatic hypotension, symptomatic sinus bradycardia, sepsis
622-201	NAT 0.030	44/A/F/III	Fatigue
387-201	NAT 0.030	49/H/F/IV	Claustrophobia
488-201	NAT 0.030	61/C/M/III	Dizziness, , Asymptomatic hypotension
498-203	NAT 0.030	64/H/M/III	Death
502-208	NAT 0.030	54/C/M/III	Anxiety, dizziness, visual hallucinations, symptomatic hypotension., anginal chest pain
502-209	NAT 0.030	77/C/F/IV	Anginal chest pain
536-220	NAT 0.030	62/B/M/III	Exacerbation of CHF
551-205	NAT 0.030	67/C/M/IV	Bradycardia, cardiac arrest
554-213	NAT 0.030	43/C/F/III	Asymptomatic hypotension
560-209	NAT 0.030	67/H/F/III	Worsening CHF
560-210	NAT 0.030	46/H/F/III	Headache
567-203	NAT 0.030	51/C/M/III	Symptomatic hypotension
620-204	NAT 0.030	78/C/M/III	Worsening anemia

Abbreviations C=Caucasian B=Black A= Asian H= Hispanic Pac is=Pacific islander M=male F-female

Table 66 Early terminations.

Subject #	Tx	Time of infusion till termination	Reason	14-day status
Dobutamine				
498-204	DOB	3.5 hr	Increased heart rate and increased ectopy	Alive
502-215	DOB	3.35	Symptomatic hypotension	Alive
536-214	DOB	3.5	Multifocal PVCs	Died
554-201	DOB	2.5	Palpitations	Alive
625-202	DOB	17.5	SVT	Alive
627-209	DOB	19.15	IV infiltration	Alive
Natrecor 0.015				
352-202	0/015	21.75	Symptomatic hypotension	Alive
554-202	0.015	21.55	Symptomatic hypotension, blurred vision	Alive
554-220	0.015	4.14	Symptomatic hypotension, diaphoresis, warmth	Alive
624-201	0.015	3.14	Abdominal pain, decreased cardiac output, left hand numbness, right shoulder pain, elbow pain, non-productive cough, headache	Alive
Natrecor 0.030				
488-201	0.030	5.0	Asymptomatic hypotension	Alive
498-203	0.030	7.38	Symptomatic hypotension, eye pressure	Died
538-202	0.030	2.25	Symptomatic hypotension	Alive
549-203	0.030	15.26	Symptomatic hypotension	Alive
550-204	0.030	9.0	Asymptomatic hypotension	Alive
556-210	0.030	4.14	Sweating, anxiety, shortness of breath	Alive
580-206	0.030	5.36	Hot flashes and diaphoresis	Alive
622-201	0.030	5.17	Bitter taste in mouth, sweating, fatigue, headache and nausea	Alive
627-204	0.030	8.15	Symptomatic hypotension	Alive
635-201	0.030	6.57	Symptomatic hypotension	Alive
530-206	0.030	16.59	Symptomatic hypotension	Alive

Hospitalizations: One hundred ninety eight of the 246 treated subjects were admitted to the hospital on the day of or the day before the start of the baseline Holter. The mean duration of hospitalization approximated five days. Re-admissions, within 30 days were similar across groups.

Table 67 Description of the index hospitalization and additional hospitalizations.

	Dobutamine	Natrecor (ug/kg/min)		
	(n=83)	0.015 (n=84)	0.03 (n=79)	P-value nominal
Total Days of Hospitalization through Day 14.				
Mean ± SD	5.7 ± 3.9	5.7 ± 3.7	5.8 ± 4.0	0.9
Median (range)	4.0 (2-15)	5.0 (2-15)	4.0 (2-15)	0.9
2-3 days	28 (34%)	29 (35%)	32 (41%)	
4-5 days	24 (29%)	22 (26%)	16 (20%)	
6-7 days	13 (16%)	16 (19%)	9 (11%)	
8-14 days	10 (12%)	10 (12%)	14 (18%)	
Not Discharged by day 14	8 (10%)	7 (8%)	8 (10%)	
Number Discharged who were readmitted	7/75 (9%)	5/77 (6%)	9/71 (13%)	0.5
1 readmission	5	5	9	
2 readmission	2	0	0	
Reason for readmission				
CHF (acute)	6	3	4	
CHF (elective)	0	0	0	
Other (acute)	2	2	2	
Other Elective)	1	0	3	

Adverse Events: Adverse events during the first 24-hours of the infusion are shown in table 68.

Table 68 Adverse events during the 24-hour infusion

	Dobutamine	Natrecor (ug/kg/min)		p-value (nominal)
		0.015	0.03	
Cardiovascular	34 (41%)	33 (39%)	45(57%)	0.048
Hypotension	5 (6%)	23 (27%)	35 (44%)	<0.001
Symptomatic Hypotension	2 (2%)	14 (17%)	19 (24%)	<0.001
Asymptomatic hypotension	4 (5%)	9(11%)	17 (22%)	0.005
Ventricular tachycardia	11 (13%)	5 (6%)	5 (6%)	>0.1
Sustained ventricular tachycardia	0	0	1 (1%)	>0.1
Non-sustained ventricular tachycardia	11 (13%)	5 (6%)	4 (5%)	>0.1
Ventricular extrasystoles	9 (11%)	3 (4%)	5 (6%)	>0.1
Tachycardia	11 (13%)	1 (1%)	2 (3%)	0.001
Bradycardia Events	1 (1%)	2 (2%)	4 (5%)	>0.1
Bradycardia	0	1 (1%)	0	>0.1
Sinus bradycardia	1(1%)	0	4(5%)	0.03
Nodal arrhythmia	0	1 (1%)	0	>0.1
Angina pectoris	3 (4%)	2 (2%)	1 (1%)	>0.1
Bigeminy	3 (4%)	1 (1%)	1 (1%)	>0.1
Body as a whole	13 (16%)	14 (17%)	14 (18%)	>0.1
Headache	2 (2%)	7 (8%)	8 (10%)	>0.1
Injection site reaction	6 (7%)	1 (1%)	2 (3%)	>0.1
Abdominal pain	1 (1%)	2 (2%)	3 (4%)	>0.1
Nervous	6(7%)	16(19%)	13 (16%)	0.061
Dizziness	3(4%)	9 (11%)	9(11%)	>0.1
Anxiety	1 (1%)	2 (2%)	3(4%)	>0.1
Insomnia	1 (1%)	2(2%)	3(4%)	>0.1
Digestive	5(6%)	12(14%)	15(19%)	0.037
Nausea	3(4%)	7(8%)	14(18%)	0.011
Vomiting	0	4(5%)	3(4%)	>0.1
Metabolic and nutritional disorders	6(7%)	5(6%)	2(3%)	>0.1
Hypokalemia	2(2%)	3(4%)	1(1%)	>0.1
Skin and appendages	2(2%)	5(6%)	5(5%)	>0.1
Sweating	1(1%)	2(2%)	3(4%)	>0.1
Respiratory	0	3 (4%)	6(8%)	0.02
Cough increased	0	2(2%)	3(4%)	>0.1
Dyspnea	0	1(1%)	2(3%)	>0.1
Musculoskeletal	3(4%)	3(4%)	0	0.07
Leg cramps	3 (4%)	0	0	0.07

Hypotension both symptomatic and asymptomatic is increased among those taking Natrecor. On the other hand, tachycardia and other measurements of ectopy are increase in the dobutamine-treated subjects. Adverse events reflected “nervous system” trend higher in the Natrecor treatments and reflect largely the increase in dizziness among those treated with Natrecor. There were more adverse events in the “digestive” system among those treated with Natrecor, reflecting an in crease in nausea and vomiting. “Respiratory” adverse events were also increased among those treated with Natrecor.

Hypotension: Specifics of hypotension are shown in Table 69.

Table 69 Description of All Hypotensive events

	Dobutamine	Natrecor (ug/kg/min)		P-value
		0.015	0.03	
Greatest Severity				0.000
No hypotension reported	78 (94%)	61 (73%)	44 (56%)	
Mild	1(1%)	9(11%)	14(18%)	
Moderate	2(2%)	14(17%)	17(22%)	
Severe	2(2%)	0	4(5%)	
Greatest effect on study drug				0.000
None/increased	1(1%)	4(5%)	10(13%)	
Dose decreased/interrupted	3(4%)	15(18%)	16(20%)	
Discontinued	1(1%)	4(5%)	9(11%)	
Onset of hypotension	?	?	?	
Duration of hypotension	?	?	?	

? = no data submitted

Laboratory:

Chemistries: Laboratory values were collected at baseline and within 24 hours of the discontinuation of the infusion. Na, K, CO2, Cl, creatinine and Bun were also to be collected between 10-14 days post enrollment. The results are shown below.

Table 70 Laboratory values at baseline and change from baseline mean ± SD.

		Dobutamine			Natrecor					
					0.015 ug/kg/min			0.03 ug/kg/min		
		B'Line	Day 2	Day 14	B'Line	Day 2	Day 14	B'Line	Day 2	Day 14
BUN	N=/(missing)	83 (0)	76 (7)	72 (11)	84 (0)	79 (5)	74 (10)	78 (1)	70 (9)	64 (15)
	Value	32.9 ± 17	-0.8 ± 7.0	6.4±16.7	35.4 ± 27.2	**2.1 ± 9.1***	2.8 ± 14.5	33.1 ± 21.9	**2.6 ± 8.3***	2.3 + 23.0
Creat.	N=/(missing)	83 (0)	77 (6)	72 (11)	84 (0)	79 (5)	74 (10)	78 (1)	74 (5)	64 (15)
	Value	1.5 ± 0.7	0.0 ± 0.3	0.1 ± 0.4	1.6 ± 0.8	0.1 ± 0.4	0.1 ± 0.4	1.5 ± 0.9	**0.1 ± 0.3***	0.1 + 0.6
CO2	N=/(missing)	78 (3)	40 (41)	NA	78 (5)	53 (30)	NA	76 (3)	48 (31)	NA
	Value	28.9 ± 4.6	-0.2 ± 2.5	NA	28.0 ± 3.4	-0.6 ± 3.1	NA	27.9 ± 4.7	0.3 ± 3.7	NA
Ca	N=/(missing)	79 (3)	48 (34)	NA	81 (1)	63 (19)	NA	71 (6)	50 (27)	NA
	Value	8.9 ± 0.5	-0.2 ± 0.4	NA	9.0 ± 0.7	-0.1 ± 0.4	NA	8.9 ± 0.5	-0.3 ± 0.5	NA
Mg	N=/(missing)	82 (1)	55 (28)	NA	83 (1)	70(14)	NA	71 (6)	57 (20)	NA
	Value	2.1 ± 0.3	0.1 ± 0.29	NA	2.1 ± 0.3	0.0 ± 0.2	NA	2.1 ± 0.3	-0.0 ± 0.3	NA
Na+	N=/(missing)	83 (0)	80 (3)	72 (11)	84 (0)	82 (2)	75 (9)	78 (1)	74 (5)	64 (15)
	Value	138 ± 4.6	-1.4 ± 2.7	-0.5 ± 4.2	138± 4.2	-1.6 ± 3.1	-0.6 ±3.5	138 ± 4.8	-1.8 ± 4.1	- 0.8 + 4.2
K+	N=/(missing)	83 (0)	81 (2)	72 (11)	84 (0)	82 (2)	75 (9)	78 (1)	76 (3)	65 (14)
	Value	4.2 ± 0.5	0.1 ± 0.5	0.4 ±0.7	4.2 ±0.4	0.2 ± 0.6	0.3 ± 0.6	4.3 ± 0.5	0.1 ±0.7	0.1 + 0.8
Cl^-	N=/(missing)	83 (0)	44 (39)	NA	84 (0)	56 (28)	NA	78 (1)	52 (27)	NA
	Value	99.6 ± 6.2	-1.3 ± 2.8	NA	100.3 ± 5.1	-1.3 ±3.0	NA	100.0 ± 5.8	-1.3 ± 4.6	NA

*Nominal p-value < 0.05.

There was a nominally significant increase in BUN for both Natrecor doses relative to dobutamine at day 2. There was also an increase in creatinine in the high dose Natrecor dose group relative to dobutamine on day 2.

This reviewer considered those subjects whose creatinine increased by> 0.5 mg/dL during any of the measurements. There were a total of 38 subjects whose creatinine increased by this value at some time during the study period. Of these subjects, 14 were in the Natrecor 0.015 g/kg/min group and 15 were in the 0.03 ug/kg/min Natrecor subjects. There were a total of 9 subjects in the dobutamine group that had increases in creatinine values of > 0.5 mg/dL. The median baseline value among those whose creatinine increased during the study was approximately equivalent to the

value of those at baseline. There did not appear to be an increased risk of a 0.5mg/dl increase among those with higher baseline creatinine values.

Among those treated with Natrecor, substantial increases in creatinine occurred earlier than among dobutamine-treated subjects. The first abnormal value occurred more frequently during the first week among Natrecor treated subjects than in the dobutamine treated subjects (Nat 0.015= 7; Nat 0.03 =7, Dobutamine =2). The number with abnormal values at the last measurement were Natrecor 0.015 ug/kg/min =8; Nat 0.03 ug/kg/min = 9; Dobutamine=7.

Table 71 Subjects with increase in creatinine of 0.5 mg/dl (Bold still > 0.5 above baseline at last visit). A √ reflects those whose value was abnormal within the first week.

pt #	Tx	baseline Value	first value inc > 0.5 mg/dl (day)	worst creatinine (day)	last creatinine (day)
554-202	0.015	0.9	1.9 (2) √	1.9 (2)	0.8 (12)
488-205	0.015	1	1.6 (6) √	1.6 (6)	1.0 (12)
560-205	**0.015**	**1.1**	**2.1 (14)**	**2.1 (14)**	**2.1 (14)**
554-220	0.015	1.3	2.0 (2) √	2.0 (2)	1.0 (10)
539-211	0.015	1.4	2.2 (2) √	2.2 (2)	1.6 (10)
387-202	0.015	1.5	2.7 (2) √	2.7 (2)	1.4 (14)
626-203	**0.015**	**1.6**	**2.2 (34)**	**2.2 (34)**	**2.2 (34)**
498-202	**0.015**	**1.6**	**2.5 (15)**	**2.5 (15)**	**2.5 (15)**
352-202	**0.015**	**2.1**	**3.7 (2)** √	**3.7 (2)**	**2.9 (31)**
626-204	**0.015**	**2.2**	**3.3 (5)** √	**3.3 (5)**	**3.3 (13)**
369-210	**0.015**	**4.1**	**5.0 (16)**	**5.0 (16)**	**5.0 (16)**
355-202	**0.015**	**4.3**	**5.4 (13)**	**5.4 (13)**	**5.4 (13)**
627-210	**0.015**	**5.4**	**6.2 (18)**	**6.2 (18)**	**6.2 (18)**
357-202	0.03	1	1.7 (7)	1.7 (7)	0.8 (13)
306-203	**0.03**	**1.1**	**2.2 (11)**	**2.2 (11)**	**2.2 (11)**
554-213	0.03	1.2	2.0 (3) √	2.0 (3)	1.0 (10)
535-202	0.03	1.3	1.9 (5) √	1.9 (5)	1.1 (13)
549-203	0.03	1.3	2.0 (3) √	2.0 (3)	1.8 (15)
605-205	**0.03**	**1.4**	**2.0 (2)** √	**2.0 (2)**	**2.0 (2)**
560-206	0.03	1.4	2.3 (2) √	2.3 (2)	1.6 (14)
487-201	**0.03**	**1.5**	**2.4 (14)**	**2.4 (14)**	**2.4 (14)**
538-202	**0.03**	**1.6**	**2.3 (14)**	**2.4 (14)**	**2.3 (14)**
635-202	**0.03**	**1.7**	**2.5 (11)**	**2.5 (11)**	**2.5 (11)**
352-203	**0.03**	**2.4**	**4.6 (11)**	**4.6 (11)**	**4.6 (11)**
536-220	**0.03**	**2.5**	**3.1 (11)**	**3.1 (11)**	**3.1 (11)**
370-202	**0.03**	**2.8**	**3.4 (13)**	**3.4 (13)**	**3.4 (13)**
554-203	**0.03**	**5.4**	**6.8 (3)** √	**6.8 (3)**	**6.6 (11)**
360-201	0.03	6.9	7.8 (2) √	7.8 (2)	3.9 (9)
620-203	**DOB**	**1.1**	**1.7 (7)**	**1.7 (7)**	**1.7 (14)**
627-209	**DOB**	**1.1**	**2.3 (15)**	**2.3 (15)**	**2.3 (15)**
580-202	**DOB**	**1.2**	**2.8 (14)**	**2.8 (14)**	**2.8 (14)**
620-202	**DOB**	**1.3**	**2.1 (7)**	**2.4 (15)**	**2.4 (15)**
580-201	**DOB**	**1.3**	**2.7 (13)**	**2.7 (13)**	**2.7 (13)**
516-202	**DOB**	**1.4**	**2.4 (4)** √	**2.4 (4)**	**2.4 (4)**
369-206	DOB	1.4	2.5 (7)	2.5 (7)	1.0 (13)
560-216	**DOB**	**2.6**	**3.8 (2)** √	**3.9 (15)**	**3.9 (15)**
627-208	**DOB**	**3.6**	**4.5 914)**	**4.5 (15)**	**4.5 (15)**

Hematology: values were collected at baseline and day 2. No results were submitted.

Urinalyses: were neither collected nor analyzed.

Vital signs: Vital signs were measured at baseline 15 and 30 minutes and 3, 8, 16, 24 hours and within 24 hours of discontinuation of study drug. The sponsor tabulated only systolic blood pressure and heart rate. The results of the two parameters are shown below. There is a substantial drop in systolic blood pressure that appears to stabilize at between the 3 and 8-hour time point for the two Natrecor doses. For dobutamine, the blood pressure increased slightly initially but re-

approached baseline between ½ to 3 hours after the start of the infusion. Both Natrecor doses differed in the extent of blood pressure reduction relative to dobutamine (nominal p-values < 0.001) but did not differ from each other.

With respect to heart rate, for dobutamine there was an initial increase in heart rate relative to baseline, which diminishes over time. For the Natrecor doses, despite the large drop in blood pressure heart rate either minimally changed or perhaps decreased. The two Natrecor doses differed (with a nominal p-value of < 0.05) only at the 3-hour time point.

Figure 18

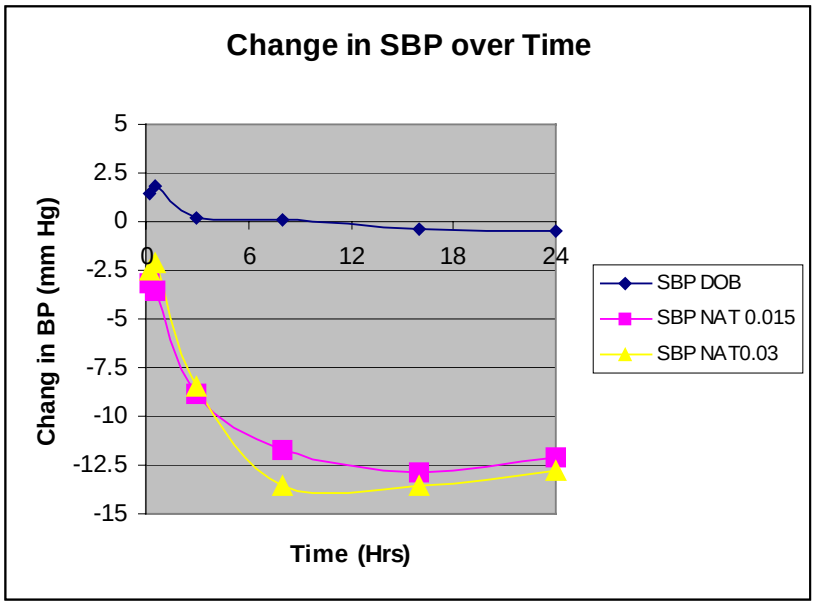
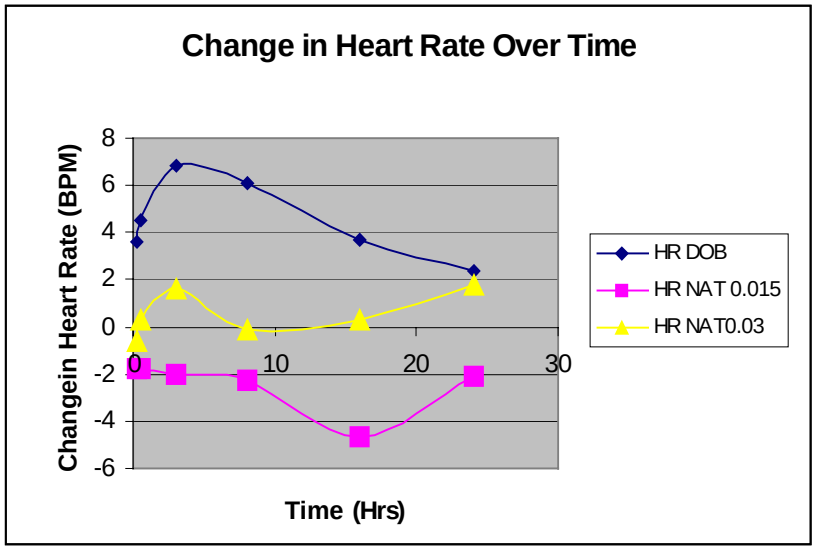


Figure 19



[Comment: It is unclear to this reviewer if the hypotension produced by Natrecor was the stimulus for worsening renal function. In particular, the substantial hypotension produced by Natrecor in conjunction with the lack of reflexive tachycardia may provoke the renal dysfunction. I've asked the sponsor to analyze whether those patients particularly with symptomatic or asymptomatic hypotensive episodes were more prone to renal dysfunction. I've also asked the sponsor to analyze the heart rate response among those who were hypotensive. Did these subjects demonstrate an increase in heart rate in response to the hypotensive episode?]

Study Summary: The PRECEDENT trial was a large multicenter study that explored the effect of dobutamine (at a goal dose of > 5 ug/min) and Natrecor at 2 doses, 0.015 and 0.030 ug/kg/min with respect to heart rate and ectopy as captured by Holter monitoring. The study was open-labeled between Natrecor and dobutamine but blinded between the two Natrecor doses. The Natrecor regimen differs from those used in other studies in that no bolus was administered.

A total of 255 subjects were enrolled. Those enrolled were to have symptomatic, decompensated CHF for which in-patient therapy was deemed appropriate. Treatment, however, could be delayed for 24 hours to collect baseline Holter data, so the degree of acute decompensation was not so severe to require immediate intervention. Most subjects enrolled were class III NYHA with a sizable proportion of class IV subjects (20-36%). Between (9-25%) of those enrolled had breathing difficulty at rest at baseline. The overall mortality at 6-months was between 16-22%, so the underlying disease was clearly severe. There was some imbalance in that a larger number of symptomatic subjects were allocated to the dobutamine group. None of those enrolled required intravenous inotropes or after-load reducers at the time of enrollment.

Dobutamine increases heart rate and increases ectopy relative to either of the Natrecor doses. The time in tachycardia over the 24-hour Holter period increased while on dobutamine, but did not substantially change while on either Natrecor dose. Ectopy as assessed, either by the number of premature ventricular beats, couplets, triplets or VT events or using the binary criteria of either the CAPS study or those of Velebit, was more frequent on dobutamine treatment than on Natrecor treatment.

Relative to baseline, symptoms improved both at 3 and 24 hours of infusion for all treatments. The treatments did not differ from each other.

With respect to safety, there were relatively few deaths at either 1- or 6- months of treatment. Numerically, the trends favored Natrecor.

There were no differences in duration of index hospitalization or in the number of hospitalization in the 14 days post infusion.

Hypotension was a prominent adverse event among those treated with Natrecor in a dose dependent manner. Hypotensive events (both symptomatic and asymptomatic) were classified as adverse events in 27% and 44% of those treated with Natrecor 0.015 and 0.03 ug/kg/min, respectively. The corresponding rate among those treated with dobutamine was 6%. Hypotension was the reason for early termination in 3, 8 and 1 patient in the Natrecor 0.015, Natrecor 0.03 and

dobutamine groups, respectively. This reviewer is awaiting the specifics of the hypotension from the sponsor. Means SBP changes (the DBP were not analyzed) decreased from baseline by 12-14 mm Hg in the Natrecor treated groups and were essentially unchanged in the dobutamine group. There was no reflex tachycardia.

Renal function was adversely altered by Natrecor treatment. Group-mean values for creatinine were significantly increased for the Natrecor 0.03 ug/kg/min dose, and trended to higher values for the low dose Natrecor group compared to dobutamine. Numerically, more Natrecor subjects had substantial (> 0.5 mg/dL) increases in creatinine at one or more measurements.

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/s/

Abraham Karkowsky
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